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(54) Title: NUCLEIC ACID ENCODING HUMAN NEURONAL CALCIUM CHANNEL SUBUNITS

(57) Abstract

Nucleic acids encoding each of three subunits, a1B, a2d, and b3, of a calcium channel, are disclosed. Also disclosed are vectors containing the nucleic acids encoding the subunits; host cells containing the nucleic acids encoding the subunits; methods of isolating nucleic acids encoding related calcium channel subunits; the subunit proteins; fusion proteins comprising the subunit proteins; antibodies to the subunit proteins; assays to identify agents that modulate calcium channel activity, and agents identified thereby; methods of treating certain central nervous system disorders by altering calcium channel activity; and methods of diagnosing diseases associated with particular calcium channels, such as Lambert-Eaton syndrome.

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Nucl ic Acid Encoding Human Neuronal Calcium Channel Subunits

Background of the Invention

Calcium channels are multi-subunit protein complexes that span the plasma membrane and are involved in the movement of calcium ions into the cell. Voltage-dependent calcium channels, the most common type of calcium channels, are classified as L-, T-, N-, or P-type channels, based on conductance levels, sensitivity to agonists and antagonists, and holding potential (K. Dunlap *et al.*, *Trends Neurosci.* *18*:89-98 (1995)). Calcium channels contain two large subunits, a1 and a2, having molecular weights between about 130 and about 200 kDa, and one to three smaller subunits, such as b, and/or g subunits, each having a molecular weight that is usually less than about 60 kDa. At least one of the large subunits is glycosylated, and a smaller subunit may be glycosylated as well. Subunit a1 is approximately 200 to about 230 kDa, based on sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE). This subunit forms the pore through which calcium enters cells. Subunit a2 is approximately 160 to 190 kDa under non-reducing conditions on SDS-PAGE. The b subunit is about 52 to 65 kDa (SDS-PAGE); it is insensitive to reducing conditions. The g subunit, which is not observed in nervous tissue or in other certain preparations, is a glycoprotein of approximately 30 to 33 kDa (SDS-PAGE).

Investigation of particular calcium channel subtypes is rendered difficult by the presence of a mixture of different tissue-specific types of calcium

channels in cells. Study of particular subtypes is essential, however, because of the importance of intracellular calcium levels in contributing to vital cellular processes including neurotransmitter release, muscle contraction, pacemaker activity, and secretion of hormones and other substances. A need remains for identifying and studying individual calcium channel subtypes.

Summary of the Invention

The current invention pertains to the isolation and sequencing of nucleic acids encoding three subunits of human N-type calcium channel: an a1B subunit, an a2d subunit, and a b3 subunit. Previously unknown alterations are present in the sequence of nucleotides encoding each of the subunits. The nucleic acid encoding the a1B subunit has a change from G to A at position 194; a change from T to G at position 2559; a change from G to A at position 6470; and a deletion of nucleotides 4814-4819. The nucleic acid encoding the a2d subunit has a change from A to C at position 329; a change from G to C at position 1191; a change from G to C at position 1219; a change from T to C at position 1596; a change from T to C at position 1980; a change from A to G at position 2090; and a change from A to G at position 3261. The nucleic acid encoding the b3 subunit has a change from C to G at position 46; a TCC insertion at position 119; a change from A to T at position 203; a change from C to T at position 300; a change from C to G at position 303; a change from A to G at position 420; a change from C to T at position 438; a change from T to C at position 477; a change from T to G at position 486; a chang from G to A at position 534; a change from A to C at position 552; a change from G to T at

position 561; an ATG insertion at position 978; a change from T to A at position 1064; a change from CG to GC at positions 1283-1284; or a change from C to T at position 1308. Certain of these changes result in amino acid alterations in the encoded proteins, while others are synonymous changes.

Vectors containing the nucleic acids encoding the subunits described above have been prepared, as have host cells containing the nucleic acids. Methods of isolating nucleic acids encoding related calcium channel subunits, by employing hybridization of the nucleic acids of the invention to nucleic acid libraries, are now available by virtue of the discoveries described herein. Also available are the subunit proteins encoded by the nucleic acids, and also fusion proteins comprising the subunit proteins. Antibodies to the subunit proteins can also be generated. Assays to identify agents that modulate calcium channel activity are described, in which test cells are exposed to the agent to be tested and a calcium channel-selective ion; depolarizing the cell membrane of the test cell; detecting current flowing into the cell; and comparing the current to that of a control cell, wherein a difference in the current detected in the test cell, as compared with the current of the control cell, indicates that the agent modulates calcium channel activity. In addition, methods of diagnosing diseases associated with particular calcium channels, such as Lambert-Eaton syndrome, are described, using assays to detect the presence of calcium channel-specific antibodies in a sample from the individual suspected of having the disease.

The changes that are present in the subunits described herein may produce functional differences in the calcium channel formed by the three subunits, which will have an effect on the interaction between the calcium channels and agonists or antagonists of the channels. Furthermore, calcium channel subunits described herein are an advantageous combination, because the b3 subunit is normally found associated with an a1B subunit *in vivo;* thus, this combination closely resembles the calcium channel *in vivo*.

Brief Description of the Drawings

Figure 1 depicts the nucleic acid (SEQ ID NO. 1) and encoded amino acid (SEQ ID NO. 2) of a human a1B subunit of the human calcium channel.

Figure 2 depicts the nucleic acid (SEQ ID NO. 3) and encoded amino acid (SEQ ID NO. 4) of a human a2d subunit of the human calcium channel.

Figure 3 depicts the nucleic acid (SEQ ID NO. 5) and encoded amino acid (SEQ ID NO. 6) of a human b3 subunit of the human calcium channel.

Figure 4 is a graphic representation of average counts per minute (CPM) for omega-conotoxin GVIA-sensitive potassium-stimulated calcium uptake in cells transfected with the three human calcium channel subunits.

Detailed Description of the Invention

The current invention pertains to the isolation and identification of DNA encoding subunits of a particular calcium channel. As described in the Examples below, cDNA encoding an a1B subunit, an a2d subunit, and a b3 subunit of the human N-type calcium channel has been isolated. The cDNA clones have been inserted into expression vectors, and are stably expressed in transformed cell lines. The resulting

transformed cells express each of the three mRNA encoding the individual subunits of the N-type channel. The transformed cells show omega-conotoxin GVIA binding activity, and omega-conotoxin GVIA toxin sensitive potassium-stimulated calcium uptake, indicating that the proteins expressed by the clones are capable of forming a functioning calcium channel.

As a result of this discovery, nucleic acids encoding the three subunits, as well as vectors containing the nucleic acids encoding one or more of the subunits, host cells containing the nucleic acids encoding one or more of the subunits, and methods of isolating nucleic acids encoding related calcium channel subunits are now available. The subunit proteins, fusion proteins comprising the subunit proteins, and antibodies to the subunit proteins, as well as assays to identify agents that modulate calcium channel activity, are also described. Agents that modulate calcium channel activity can be used to treat certain central nervous system disorders by altering calcium channel activity. In addition, methods of diagnosing diseases associated with particular calcium channels, such as Lambert-Eaton syndrome, are described.

A "nucleic acid encoding a calcium channel subunit", as used herein, is a sequence of nucleotides which encodes either an a1B subunit, an a2d subunit, or a b3 subunit of the N-type calcium channel. Nucleic acid encoding a calcium channel subunit can be either cDNA, DNA or mRNA. The nucleic acid encoding a calcium channel subunit is "isolated," indicating that it has been purified according to standard techniques known in the art (for example, such as by techniques described by Sambrook *et al.* (eds), in Molecular

Cloning: A Laboratory Manual, (2nd ed.), Cold Spring Harbor Laboratory Press (1989)).

In one embodiment, nucleic acid encoding a calcium channel a1B subunit has the sequence of nucleotides shown in Figure 1 (SEQ ID NO. 1). In another embodiment, nucleic acid encoding a calcium channel a1B subunit is a nucleic acid encoding a functional equivalent of the subunit encoded by sequence of nucleotides shown in Figure 1 (SEQ ID NO. 1). A "functional equivalent" has the same function as the calcium channel subunit, but is encoded by a nucleic acid that may have minor variations in the sequence of nucleotides, in comparison to the nucleic acid encoding the subunit. A nucleic acid encoding a functional equivalent is referred to herein as an "equivalent" nucleic acid. Minor variations in equivalent nucleic acids include variations that result in no alteration of the encoded amino acid sequence (synonymous changes); variations that result in conservative amino acid substitutions in the encoded amino acid sequence; and/or minor deletions or insertions of nucleotides that do not alter the activity of the peptide. Such changes are readily known to the skilled artisan. For example, representative conservative amino acid changes include: alanine to glycine or serine; arginine to lysine; asparagine to glutamine or histidine; cysteine to serine; glutamine to asparagine; glutamate to aspartate; glycine to alanine or proline; histidine to asparagine or glutamine; isoleucine to leucine or valine; leucine to isoleucine or valine; lysine to arginine or glutamine; methionine to leucine tyrosine, or isoleucine; phenylalanine to methionine, leucine to tyrosine; serine to threonine; threonine to serine;

tryptophan to tyrosine; tyrosine to tryptophan or phenylalanine; valine to isoleucine or leucine.

A functional equivalent of a subunit has an activity that is equivalent to the subunit. "Activity" refers to the ability of the peptide to form a functional calcium channel with other necessary subunits. A functional calcium channel is a calcium channel that is able to provide for and regulate entry of calcium channel-selective ions, including calcium, in response to appropriate stimuli, and/or is able to bind ligands having affinity for the calcium channel. The activity of a calcium channel may be assessed *in vitro* by standard methods, such as electrophysiological or other methods described below.

Nucleic acids encoding a functional equivalent of a calcium channel a1B subunit, include at least one of the following alterations, in comparison to the nucleic acid sequence in the HSCACHNT Genbank file (see Ellis, S.B. *et al., Science 257*:389-395 (1992)): a change from G to A change at position 194; a change from T to G at position 2559; a change from G to A at position 6470; or a deletion of nucleotides 4814-4819. The nucleic acid having the sequence of nucleotides shown in Figure 1 (SEQ ID NO. 1), as well as nucleic acids encoding a functional equivalent of the subunit encoded by the sequence of nucleotides shown in Figure 1 (SEQ ID NO. 1), are collectively referred to herein as a nucleic acid encoding a calcium channel a1B subunit.

A nucleic acid encoding a calcium channel a2d subunit has the sequence of nucleotides shown in Figure 2 (SEQ ID NO. 3), or a s quence of nucleotides encoding a functional equivalent of the subunit encoded by the nucleic acid shown in Figure 2 (SEQ ID

NO. 3). A nucleic acid encoding a functional equivalent of the subunit encoded by the sequence of nucleotides shown in Figure 2 (SEQ ID NO. 3) includes at least one of the following alterations, in comparison to the HSCACNLB EMBL file (Harpold, M.M. *et al., Neuron 8*:71-84 (1992)): a change from A to C at position 329; a change from G to C at position 1191; a change from G to C at position 1219; a change from T to C at position 1596; a change from T to C at position 1980; a change from A to G at position 2090; or a change from A to G at position 3261.

A nucleic acid encoding a calcium channel b3 subunit has the sequence of nucleotides shown in Figure 3 (SEQ ID NO. 5), or the sequence of nucleotides encoding a functional equivalent of the subunit encoded by the nucleic acid shown in Figure 3 (SEQ ID NO. 5). A sequence of nucleotides encoding a functional equivalent of the subunit encoded by the nucleic acid shown in Figure 3 (SEQ ID NO. 5) includes at least one of the following alterations, in comparison to the HUMCALBA Genbank file (see Collin, T. *et al., Eur. J. Biochem. 220(1)*:257-262 (1994)): a change from C to G at position 46; a TCC insertion at position 119; a change from A to T at position 203; a change from C to T at position 300; a change from C to G at position 303; a change from A to G at position 420; a change from C to T at position 438; a change from T to C at position 477; a change from T to G at position 486; a change from G to A at position 534; a change from A to C at position 552; a change from G to T at position 561; an ATG insertion at position 978; a change from T to A at position 1064; a change from CG to GC at positions 1283-1284; or a change from C to T at position 1308.

The nucleic acids encoding calcium channel subunits of the invention can be used to isolate other nucleic acids encoding related subunits. For example, all or a portion of one of the nucleic acids encoding a calcium channel subunit can be used as a probe to isolate nucleic acids from a nucleic acid library by hybridization techniques. A "portion" of the nucleic acid indicates a part of the nucleic acid that contains one of the specific alterations described above. Stringency conditions should be tailored to eliminate hybridization of the probes to extraneous nucleic acid sequences (see Sambrook *et al.* (eds), Molecular Cloning: A Laboratory Manual, (2nd ed.), Cold Spring Harbor Laboratory Press (1989), particularly chapter 11.45). In a preferred embodiment, stringency conditions are selected such that the nucleic acid encoding a calcium channel subunit, or a portion of the nucleic acid, selectively hybridizes to a second nucleic acid (the target nucleic acid). "Selective hybridization" indicates that the hybridization is of sufficient specificity to allow the target nucleic acid to be identified or isolated from other nucleic acids. Generally, medium stringency conditions will allow selective hybridization. Nucleic acids that encode a calcium channel subunit, and are capable of selectively hybridizing, under medium or high stringency conditions, to all or a portion of a nucleic acid encoding a calcium channel subunit of the invention, or to all or a portion of a nucleic acid encoding a functional equivalent of a calcium channel subunit of the invention, are also encompassed by the invention.

Nucleic acids encoding a calcium channel a1B subunit, a calcium channel a2d subunit, or a calcium

channel b3 subunit, as described above, can be inserted into a vector to facilitate expression. The vector is capable of expressing nucleic acids that are in operative linkage with endogenous or exogenous regulatory sequences; it may be a plasmid, a phage, a virus, or other vector. The vector can contain other elements, such as transcriptional promoter elements, enhancer elements, splicing signals, termination and polyadenylation signals, viral replicons, and/or bacterial plasmid sequences. Upon introduction of the vector into a host cell, the nucleic acid inserted into the vector is expressed. The vector can contain more than one nucleic acid encoding a calcium channel subunit of the invention. For example, a vector can contain nucleic acids encoding a calcium channel a1B subunit, as well as nucleic acids encoding a calcium channel a2d subunit. If only one subunit is used, it is understood that other known sequences are present to encode a functional protein.

A vector containing the nucleic acids encoding a calcium channel subunit of the invention, as described above, can be transformed or transfected into an appropriate host cell for expression. Alternatively, a nucleic acid encoding a calcium channel subunit of the invention can be inserted directly into the host cell. The nucleic acids can be introduced into the cell in a manner such that they are integrated into the host cell genome; alternatively, they can be maintained episomally.

Representative host cells include *Escherichia coli*, HEK 293 cells, Chinese hamster ovary (CHO) cells, African green monkey cells, mouse L cells, amphibian oocytes, and CHODUX cells (Mitchell, P.J. *et al., Mol. Cell Biol.* 6(6)1926-35 (1986)). In a

preferred embodiment, the host cell does not naturally contain nucleic acids encoding, or produce calcium channels comprising, a1B, a2d, or b3 subunits, in order to facilitate distinguishing the nucleic acids and encoded subunits of the invention from other, native nucleic acids and subunits. In a more preferred embodiment, the host cell does not express or produce endogenous calcium channel subunits of the type, or in an amount, that substantially interferes with detection of the nucleic acids and encoded subunits of the invention.

A single a1 subunit is sufficient to form a calcium channel; therefore, at least the nucleic acid encoding the a1B subunit is introduced into the host cell. In a preferred embodiment, nucleic acids encoding each of the three subunits are introduced into the host cell such that the host cell expresses the subunits and includes one or more of them in membrane-spanning calcium channels. In a preferred embodiment, the host cell expresses functional calcium channels that are capable of controlling movement of calcium channel-selective ions and/or binding compounds. In a more preferred embodiment, the calcium channels are composed substantially or entirely of the three subunits encoded by the nucleic acids of the invention, in order to generate a calcium channel that is closer to the normal physiologic state of the channel in the mammalian central nervous system. A host cell which has been transformed or transfected as described above is also referred to herein as a transformed cell.

Host cells transformed or transfected with nucleic acids encoding one or more of the calcium channel subunits of the invention can be used for

screening for compounds that modulate calcium channel activity. Because the host cells have a homogeneous population of calcium channels, they provide a means to identify agents that specifically modulate activity of the particular calcium channels. An agent that modulates (e.g., enhances or upregulates, or inhibits or downregulates) calcium channel activity is an agent that affects the ability of the calcium channel to pass calcium channel-selective ions, or affects other detectable calcium channel characteristics, such as current kinetics. The agent may affect the calcium channel directly or indirectly.

For example, transformed cells can be used in assays that identify agents that are agonists or antagonists of calcium channel activity. To identify agents that modulate calcium channel activity, a transformed cell (or a culture of transformed cells), used as a "test" cell, is maintained in a solution containing an agent to be tested for its ability to modulate calcium channel activity (the test agent) and a calcium channel selective ion. A "calcium channel selective ion" refers to an ion that is capable of flowing through, or being blocked from flowing through, a calcium channel which spans a cellular membrane under conditions which would permit or block the flow of calcium ions. Ba^{2+} is an example of a calcium channel selective ion. The cell membrane of the test cell is then depolarized, and current flowing into the test cell is detected. If the current that is detected is different from the current produced by depolarizing the same cell or a control cell in the presence of the same calcium channel selective ion, but in the absence of the compound, then the agent modulates calcium channel activity. In a preferred

embodiment, the test cell is maintained at a holding potential which substantially inactivates calcium channels prior to the depolarization step. If the current is higher in the presence of the agent than in the absence of the agent, then the agent is an agent that enhances calcium channel activity (a calcium channel agonist). If the current is lower in the presence of the agent than in the absence of the agent, then the agent is an agent that inhibits calcium channel activity (a calcium channel antagonist).

One "control" cell which can be used as described above, is a cell that is maintained in substantially the same manner as the test cell, with the exception that the control cell is not exposed to the agent to be tested. An alternative "control" cell is a cell which is identical to the test cell, except that it does not express functional calcium channels.

Agents identified by these methods can be used to modulate activity of calcium channels *in vivo*. The *in vitro* assays described above should accurately predict relative efficacy of an agent as an agonist or an antagonist of calcium channels, since the calcium channel subunits described herein are subtype and tissue-specific. Specific disease targets include central nervous system disorders, including stroke, cerebral ischemia, epilepsy, chronic pain, head trauma, and other central nervous system diseases or conditions in which too much or too little neurotransmitter is released. The agent is administered by an appropriate route, such as orally, subcutaneously, transdermally, intravenously, intramuscularly, intraperitoneally, topically, rectally, vaginally, nasally, or via an implanted

reservoir. The agent can be administered in dosage formulations containing conventional, non-toxic, physiologically-acceptable carriers, adjuvants, and/or vehicles. The formulation in which the agent is administered will depend at least in part on the route by which it is administered. The agent is administered in an effective amount, which is that amount necessary to alleviate, reduce, eliminate, or prevent the symptoms associated with the disease, disorder or condition to be treated. More than one agent can be administered; if more than agent is used, the effective amount is that amount of the combination of agents that is necessary to alleviate, reduce, eliminate or prevent the symptoms associated with disease, disorder or condition. The effective amount will be determined on an individual basis, and will be based in part, on consideration of the particular agent, the individual's size and gender, the severity of the symptoms to be treated, the result sought, and the disease, disorder or condition to be treated. The effective amount can be administered in a series of doses separated by appropriate intervals, such as hours, days, or weeks. Alternatively, the effective amount can be administered as a sustained release dose, such as by a controlled-release dosage formulation.

Purified proteins encoded by a nucleic acid encoding a calcium channel a1B subunit, a calcium channel a2d subunit, or a calcium channel b3 subunit, as described above, are also described. The proteins (also referred to herein as calcium channel subunits of the invention) can be isolated from a host cell transfected or transformed with the nucleic acid encoding the subunit. Representative proteins include

a calcium channel a1B subunit having the amino acid sequence shown in Figure 1 (SEQ ID NO. 2); a calcium channel a2d subunit having the amino acid sequence shown in Figure 2 (SEQ ID NO. 4); or a calcium channel b3 subunit having the amino acid sequence shown in Figure 3 (SEQ ID NO. 6).

Fusion proteins comprising the calcium channel a1B subunit, a calcium channel a2d subunit, or a calcium channel b3 subunit can also be generated using standard techniques. For example, a fusion nucleic acid can be generated by splicing, or attaching the nucleic acid encoding the calcium channel subunit to a nucleic acid encoding another protein or peptide (the fusion partner or protein), or by inserting the nucleic acid encoding the calcium channel subunit and the fusion protein into a common vector; the fusion nucleic acid can then be transformed, transfected, or inserted into a host cell for transcription and translation.

Antibodies (or immunoglobulins) to the calcium channel subunits of the invention can be generated. The term "antibody", as used herein, encompasses both polyclonal and monoclonal antibodies, as well as mixtures of more than one antibody reactive with a calcium channel subunit of the invention (e.g., a cocktail of different types of monoclonal antibodies reactive with the mutant protein or protein fragment). The term antibody is further intended to encompass whole antibodies and/or biologically functional fragments thereof, chimeric antibodies comprising portions from more than one species, humanized antibodies, human-like antibodies, and bifunctional antibodies. Biologically functional antibody fragments which can be used are those fragments

sufficient for binding of the antibody fragment to the calcium channel subunit of interest. Once the antibodies are raised, they are assessed for the ability to bind to the calcium channel subunit of interest. Conventional methods can be used to perform this assessment. Antibodies can also be raised to calcium channels formed by the combination of the calcium channel a1B subunit, the calcium channel a2d subunit, and the calcium channel b3 subunit described herein.

The chimeric antibodies can comprise portions derived from two different species (e.g., a constant region from one species and variable or binding regions from another species). The portions derived from two different species can be joined together chemically by conventional techniques or can be prepared as single contiguous proteins using genetic engineering techniques. DNA encoding the proteins of both the light chain and heavy chain portions of the chimeric antibody can be expressed as contiguous proteins.

Monoclonal antibodies (mAb) reactive with a calcium channel subunit of the invention, or a calcium channel formed by the subunits, can be produced using somatic cell hybridization techniques (Kohler and Milstein, *Nature 256*: 495-497 (1975)) or other techniques. In a typical hybridization procedure, purified calcium channel subunit, or calcium channels, can be used as the immunogen. An animal is immunized with the immunogen to obtain antibody-producing spleen cells. The species of animal immunized will vary depending on the specificity of mAb desired. The antibody producing cell is fused with an immortalizing cell (e.g., a myeloma cell) to create a hybridoma

capable of secreting antibodies. The unfused residual antibody-producing cells and immortalizing cells are eliminated. Hybridomas producing desired antibodies are selected using conventional techniques and the selected hybridomas are cloned and cultured.

Polyclonal antibodies can be prepared by immunizing an animal in a similar fashion as described above for the production of monoclonal antibodies. The animal is maintained under conditions whereby antibodies reactive with the calcium channel subunit of interest, or the calcium channel, are produced. Blood is collected from the animal upon reaching a desired titer of antibodies. The serum containing the polyclonal antibodies (antisera) is separated from the other blood components. The polyclonal antibody-containing serum can optionally be further separated into fractions of particular types of antibodies (e.g., IgG, IgM).

Antibodies that are specific for the calcium channel subunits of the invention, or for the calcium channel formed by the three subunits of the invention, can be used for immunohistochemistry to monitor distribution and expression density of the various subunits, or of the calcium channels themselves, in different tissues, including in normal and in diseased tissue. The antibodies can also be used as a therapeutic agent, in order to modulate calcium channel activity, as described in detail above.

Antibodies that are specific for the calcium channel subunits of the invention, or for the calcium channel formed by the three subunits of the invention, can also be used to facilitate diagnosis of Lambert-Eaton Syndrome (LES). LES autoimmune disease is characterized by insufficient release of acetylcholine

from motor nerve terminals which normally are responsive to nerve impulses. IgG from LES patients block individual voltage-dependent calcium channels and thus inhibit calcium channel activity (Kim and Neher, *Science 239*:405-8 (1988)). To diagnose LES, a test sample of blood or other bodily fluid is obtained from an individual suspected of having or carrying the disease. The test sample is contacted with a calcium channel subunit of the invention, or a calcium channel formed by the three subunits of the invention, under conditions which would allow any antibody which is specific for the calcium channel subunit or the calcium channel, and which may be present in the test sample, to bind. Binding of antibody to the calcium channel subunit of the invention, or the calcium channel formed by the subunits of the invention, if such binding exists, is then detected. The presence of binding indicates that the individual has antibodies to the calcium channel, and thus, is afflicted with LES.

The invention is further illustrated by the following Examples.

Example 1:

Isolation and Expression of Clones for Human a1B Subunit of N-Type Channel

Sequences referred to herein are described in comparison to the sequence encoding an a1B subchannel, described in the HSCACHNT data base (see Ellis, S.B. *et al., Science 257*:389-395 (1992)).

A. Isolation of Primary Clones

Three primary clones, each containing a portion of the a_{1B} subunit, were obtained by hybridization under low stringency conditions with human cerebellum library at 50°C in 6X sodium chloride, sodium citrate

(SCC) overnight. Hybridized nucleic acids were washed using standard techniques (see Sambrook *et al.* (eds), Molecular Cloning: A Laboratory Manual, (2nd ed.), Cold Spring Harbor Laboratory Press (1989)).

First, clone pN, which spans sequences 54-1405, was cloned into the SmaI site of pSK-(Bluescript). The SacI site of the polylinker is at the 5' end. The SmaI site was destroyed. pN has a single nucleotide change (G to A at position 194), which alters the amino acid at the corresponding position in the protein from gly to ser.

The second clone, pM, spans sequences 978-4562. EcoRI/blunt fragment was inserted into EcoRI/SmaI sites of pSK-. The KpnI site of the polylinker was at the 5' end. The SmaI site was destroyed. pM has a single nucleotide change (T to G at position 2559), which results in an alteration of the amino acid at the corresponding position from leu to arg.

Clone pC, which spans sequences 4105-7322, was also isolated. An EcoRI/XbaI fragment was cloned into EcoRI/XbaI restricted pNK-CMV vector. The SacI site of the polylinker is at the 5' end. Clone pC has two changes: a single nucleotide change at position 6470 (G to A), resulting in an alteration of the corresponding amino acid from gly to ser; and a six base pair deletion at nucleic acid positions 4814-4819, resulting in a deletion of the two corresponding amino acids (glu and thr).

B. Generation of pSK-Ha1

In order to generate a clone containing the entire a1B cDNA, combination vectors were made. First, pMC was created. To allow cleavage by MamI, both pM and pC were transformed into SCS110 cells (Stratagene; dam-, dcm-), and the unmethylated DNA was isolated. pC was

digested with XbaI and MamI, and the 2930 bp fragment was isolated. pM was also digested with MamI and XbaI, and the 6.4 kb vector + insert band was isolated. These two fragments were ligated together to create pMC. The fusion point is the MamI site at position 4395.

pNMC, a fusion of pN and pMC, was then generated. pN was restricted with KpnI and XbaI, and the 1.4 kb insert was isolated. pMC was restricted with XbaI and partially restricted with KpnI. The 6012 XbaI/KpnI fragment was isolated. These two fragments were ligated together, and the ligation reaction was then cut with XbaI. The resulting fragments were then ligated to a pSK- vector restricted with XbaI. The resulting plasmid contains the entire coding sequence of a1, with 91 bp 5' UT, and 157 bp 3' UT (pos 54-7322). the fusion point is the KpnI site at position 1310. The KpnI site of the pSK- polylinker is at the 5' end. This pNMC vector is referred to as pSK-Ha1.

C. Expression Clones

Two expression clones were generated. The first, pNK-Ha1, was constructed by isolating the XbaI insert of pSK-Ha1; this XbaI insert was inserted into the XbaI site of pNK-CMV. The polylinker SacI site is at the 5' end.

A second expression clone, pNK-Ha1-Koz, was also generated. A 5' primer containing an optimized Kozak sequence (CCACCATGG) (SEQ ID NO. 7), an EcoRI site, and surrounding bases was synthesized. A 3' primer spanning the BglII site at position 1463 was also synthesized. These primers were used to PCR the a1 5' end from pNK-Ha1. This product was cut with EcoRI and BglII, and cloned into a likewise restricted pNK-Ha1 plasmid. The resulting truncated plasmid contains the

Kozak sequence and has been shown to express at least as well as the parent plasmid in transient transfection studies.

The Ha1 gene thus includes several changes from the previously known sequence presented in the HSCACHNT Genbank file. A single nucleotide change (G to A at position 194), alters the amino acid at the corresponding position in the protein from gly to ser; a single nucleotide change (T to G at position 2559), results in an alteration of the amino acid at the corresponding position from leu to arg. Also, a single nucleotide change at position 6470 (G to A), results in an alteration of the corresponding amino acid from gly to ser; and a six base pair deletion at nucleic acid positions 4814-4819, results in a deletion of the two corresponding amino acids (glu and thr). These alterations are summarized in Table I.

Table I: a1B Alterations

Position	Nucleotide Change	Amino Acid Change
194	G to A	Gly to Ser
2559	T to G	Leu to Arg
6470	G to A	Gly to Ser
4814-4819	Deletion 6 bp	Deletion Glu and Thr

Example 2:
Isolation and Expression of Clones for Human a2d Subunit of N-Type Channel

Sequences referred to herein are described in comparison to the sequence encoding an a2d subchannel, described in the HSCACNLB data base (Harpold, M.M. et *al., Neuron* 8:71-84 (1992)).

A. Isolation of Primary Clones and Generation of clone pNK-Ha2

The clone pNK-Ha2, was constructed as a fusion of two PCR clones. The template was human cerebellum QuickClone (Clonetech) cDNA, and the two PCR clones included sequences from 16-1409 (p2110) and from 1379-3313 (p2223). They were isolated as T/A clones in PCRII (Invitrogen) with the polylinker NotI site at the 5' end of each clone. p2110 was restricted with EcoRI and NsiI, and p2223 was restricted with NsiI and KpnI. The gel-purified inserts were fused at the NsiI site (Pos. 1394) and cloned into an EcoRI/KpnI restricted pNK-CMV vector. The SacI site is at the 5' end.

This clone, pNK-Ha2, contained certain alterations from a previously identified a2 sequence described in the HSCACNLB EMBL file. These alterations are summarized in Table II.

Table II: Alterations in Ha2d

Position	Nucleotide Change	Amino Acid Change
329	A to C	Ser to Arg
1191	G to C	Arg to Thr
1219	G to C	Glu to Asp
1596	T to C	Val to Ala
1980	T to C	Ile to Thr
2090	A to G	Asn to Asp
3261	A to G	Val to Ala

B. Expression Clones

Two expression clones were generated. First, pNK-Ha2 was cut with KpnI and blunt ended. EcoRI linkers were attached. The reaction was treated with EcoRI, and the 3.3 kb EcoRI insert was isolated. This

EcoRI insert was ligated into two different vectors, pED, and pBabe-CMV, which had been restricted with EcoRI. The correct orientations were selected. The resultant expression clones are referred to herein as pBabe-Ha2 and pED-Ha2.

Example 3:
Isolation and Expression of Clones for Human b_3 Subunit of N-Type Channel

Sequences referred to herein are described in comparison to the sequence encoding an b3 subchannel, described in the HUMCALBA data base Genbank file (see Collin, T. *et al., Eur. J. Biochem. 220(1)*:257-262 (1994)).

A. Isolation of Primary Clones and Generation of Clone pNK-Hb3

A blunt ended PCR product spanning sequences 21-1490 was cloned into the EcoRI site of pSK-. The template was human cerebellum QuickClone (Clonetech) cDNA, generating pSK-Hb3. The EcoRI/KpnI insert of pSK-Hb3 was isolated and subsequently subcloned into the EcoRI/KpnI sites of pNK-CMV. The SacI site of the polylinker is at the 5' end. This clone, pNK-Hb3, contained certain alterations from a previously identified b3 sequence described in the HUMCALBA Genbank file. These alterations are summarized in Table III.

Table III: Alterati ns in Hb3

Position	Nucleotide Change	Amino Acid Change
46	C to G	Leu to Val
119	TCC insertion	Ser insertion
203	A to T	Glu to Val
300	C to T	no change
303	C to G	no change
420	A to G	no change
438	C to T	no change
477	T to C	no change
486	T to G	no change
534	G to A	no change
552	A to C	no change
561	G to T	no change
978	ATG insertion	Met insertion
1064	T to A	Leu to His
1283-4	CG to GC	Thr to Ser
1308	C to T	no change

Example 4

Demonstration of Formation of Calcium Channels

CHODUX cells (Mitchell, P.J. *et al., Mol. Cell Bio. 6(6)*:1926-35 (1986), Genbank M13476, M13477) were seeded on 100 mm dishes with 1 to 2 X 10^6 cells, at 24 hours before transfection. Cells were transformed with each of the following three expression clones: pNK-Ha1, pNK-Ha2, and pNK-Hb3, using $CaPO_4$ transfection kit (Stratagene Mammalian Transfection Kit) according to the manufacturer's instructions. Cells were then washed using a single PBS wash, being careful not to dislodge cells. Thirty to 35 mg DNA was used per plate, in an approximately 2:1:1 subunit ratio (20 mg a1B, 7.5 mg a2d, 5 mg b3). Transfection was allowed to proceed for approximately 16 hours overnight.

Saturating binding experiments were performed on the cells using a protocol as described by Harpold *et*

al. (*Science* 257:389-395 (1992)). Briefly, reaction tubes containing ^{125}I-omega-conotoxin GVIA (NEN) were prepared. The ^{125}I-omega-conotoxin GVIA is packaged in vials of 10 mCi at a specific activity of 2200 Ci/mmol. The vial is resuspended in 450 ml water, to obtain 10 nM. For a 200 pM (saturating) final concentration, 10ml/0.5 ml reaction was used. Cells were washed 1X with PBS and resuspended with 1-2 ml binding buffer and BSA per plate by pipetting. Approximately 500,000 cells (50-100 ml) per 0.5 ml reaction were used to initiate binding reaction. The reaction was allowed to proceed for 30-60 minutes at 37°C. Subsequently, 1 ml cold wash buffer + BSA was added, and cells were pelleted by 5 minutes at 2.8 krpm at 4°C (Sorvall RT6000). Cells were washed 1X with 2 ml cold wash buffer + BSA and resuspended by gently vortexing; subsequently, they were repelleted. After aspiration of liquid, scintillation counting was performed.

Results of the experiments demonstrated specific omega-conotoxin GVIA binding to whole cells. Specific binding indicates that the expression clones were expressed, and that the expressed subunits formed calcium channels.

Example 5

Demonstration of Inhibition of omega-Conotoxin GVIA-Sensitive Potassium-Stimulated Calcium Uptake

The uptake of ^{45}Ca into cells was performed by an adaptation of the method of Tan, K. and A.H. Tashjian (*J. Biol. Chem. 259*:418-426 (1984). The principle of the method involves activating ion permeation through synaptosomal calcium channels by high potassium-induced depolarization of the synaptosomal preparation. The uptake of ^{45}Ca measured by this

procedure is mediated by N-type calcium channels, and is sensitive to dihydropyridine, phenylalkylamine, and benzothiazipine Ca antagonists at therapeutically relevant concentrations (Tan and Tashjian, ibid.).

Cells were transfected with the three human calcium channel subunits described herein. Transfected cells were suspended in 15 ml growth medium (Ham's F-10 medium plus 15% heat-inactivated horse serum and 2.5% heat-inactivated fetal bovine serum). The cells were centrifuged, resuspended, and then added to T-75 flasks containing 12-15 mls growth medium, and incubated at 37°C for approximately one week. The cells were then removed from the flask after dissociation from the walls of the flask by treatment for 5 minutes at 37°C with 10 mM EDTA in phosphate buffered saline. The buffer was decanted, and the cells were resuspended in approximately 200 ml of growth medium. The cells were then aliquoted 200 mg/well) into each well of several 96-well plates, and grown under the aforementioned conditions for 3-4 weeks, with replacement of growth medium occurring twice per week. Cells were fed growth medium 24 hours before they are employed for ^{45}Ca uptake determinations.

At the time of the assay, media was aspirated from each 96-well plate using a manifold designed to allow 50 mL of liquid to remain in each well. Each plate was washed and aspirated twice with a low K+ buffer solution "LKHBBS" (in mM: 5 KCl, 145 NaCl, 10 Hepes, 1 $MgCl_2$, 0.5 $CaCl_2$, 10 glucose, pH 7.4), 200 ml/well. Each plate was incubated for 10 minutes at 37°C, and aspirated as above. To each well of each plate, 50 ml of LKHBBS containing the agent in twice

the final concentration was added. The agents added are set forth in Table IV.

Table IV:

Agents Added to Transfected Cells, Demonstrating omega-Conotoxin GVIA-Sensitive Potassium-Stimulated Calcium Uptake

Sample	Cell Type	Agent Added
1	HEK293	Control (no agent)
2	HEK293	75 mM KCl
3	T9	Control (no agent)
4	T9	74 mM KCl
5	T9	SNX-111 (10 mM)
6	T9	SNX-111 (10 mM) plus KCl (negative control)
7	T9	gadolinium (10 mM)
8	T9	gadolinium (10 mM) plus KCl (negative control)

The plates were incubated for 10 minutes at room temperature. To each well of each plate, 50 ml of either of two solutions were added: (a) LKHBBS containing 1 mCi of carrier-free ^{45}Ca, or (b) HKHBBS (a high K+ buffer containing 150 mM KCl and no NaCl, but otherwise identical to LKHBBS).

Each plate was then incubated for 5 minutes at room temperature, aspirated as above, and quenched with 200 ml/well of Quench Buffer (Ca-free LKHBBS containing 10 mM Tris-EGTA). Each plate was aspirated and rinsed with Quench Buffer a second time, then carefully aspirated to dryness. To each well of each plate 100 ml of High Safe II scintillation fluid (MicroScint (Packard)) was added. The plates were sealed, shaken, and subjected to scintillation spectrophotometry on a Microbeta 96-well Scintillation Counter (Wallac, Gaithersburg, MD, USA). Averag

counts per minute (CPM) are plotted in Figure 4 (numbering of data points corresponds to the numbering of agents in Table IV). Results indicated that omega-conotoxin GVIA-sensitive potassium-stimulated calcium uptake occurred in the transfected cells, and was inhibited by the agents known to inhibit L-type calcium channels, thereby demonstrating that the three subunits formed a functioning calcium channel.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Franco, Rodrigo
Sun Chen, Ai Ru
Suey, David J.

(ii) TITLE OF INVENTION: NUCLEIC ACID ENCODING HUMAN NEURONAL CALCIUM CHANNEL SUBUNITS

(iii) NUMBER OF SEQUENCES: 6

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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
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(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Mata, Elizabeth W.
(B) REGISTRATION NUMBER: 38,236
(C) REFERENCE/DOCKET NUMBER: 96188/PCT

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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7266 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 92..7102

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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TCCGTGGCTG CTCCGCTCTG AGCGCCTGGC GCGCCCCGCG CCCTCCCTGC CGGGGCCGCT
60
GGGCCGGGGA TGCACGCGGG GCCCGGGAGC C ATG GTC CGC TTC GGG GAC GAG
112
                                  Met Val Arg Phe Gly Asp Glu
                                    1               5

CTG GGC GGC CGC TAT GGA GGC CCC GGC AGC GGA GAG CGG GCC CGG GGC
160
Leu Gly Gly Arg Tyr Gly Gly Pro Gly Ser Gly Glu Arg Ala Arg Gly
        10                  15                  20

GGC GGG GCC GGC GGG GCG GGG GGC CCG GGT CCC GGG GGG CTG CAG CCC
208
Gly Gly Ala Gly Gly Ala Gly Gly Pro Gly Pro Gly Gly Leu Gln Pro
    25                  30                  35

GGC CAG CGG GTC CTC TAC AAG CAA TCG ATC GCG CAG CGC GCG CGG ACC
256
Gly Gln Arg Val Leu Tyr Lys Gln Ser Ile Ala Gln Arg Ala Arg Thr
 40                  45                  50                  55

ATG GCG CTG TAC AAC CCC ATC CCG GTC AAG CAG AAC TGC TTC ACC GTC
304
Met Ala Leu Tyr Asn Pro Ile Pro Val Lys Gln Asn Cys Phe Thr Val
                60                  65                  70

AAC CGC TCG CTC TTC GTC TTC AGC GAG GAC AAC GTC GTC CGC AAA TAC
352
Asn Arg Ser Leu Phe Val Phe Ser Glu Asp Asn Val Val Arg Lys Tyr
            75                  80                  85

GCG AAG CGC ATC ACC GAG TGG CCT CCA TTC GAG TAT ATG ATC CTG GCC
400
Ala Lys Arg Ile Thr Glu Trp Pro Pro Phe Glu Tyr Met Ile Leu Ala
        90                  95                  100

ACC ATC ATC GCC AAC TGC ATC GTG CTG GCC CTG GAG CAG CAC CTC CCT
448
Thr Ile Ile Ala Asn Cys Ile Val Leu Ala Leu Glu Gln His Leu Pro
    105                 110                 115

GAT GGG GAC AAA ACG CCC ATG TCC GAG CGG CTG GAC GAC ACG GAG CCC
496
Asp Gly Asp Lys Thr Pro Met Ser Glu Arg Leu Asp Asp Thr Glu Pro
120                 125                 130                 135

TAT TTC ATC GGG ATC TTT TGC TTC GAG GCA GGG ATC AAA ATC ATC GCT
544
Tyr Phe Ile Gly Ile Phe Cys Phe Glu Ala Gly Ile Lys Ile Ile Ala
                140                 145                 150

CTG GGC TTT GTC TTC CAC AAG GGC TCT TAC CTG CGG AAC GGC TGG AAC
592
Leu Gly Phe Val Phe His Lys Gly Ser Tyr Leu Arg Asn Gly Trp Asn
            155                 160                 165

GTC ATG GAC TTC GTG GTC GTC CTC ACA GGG ATC CTT GCC ACG GCT GGA
640
Val Met Asp Phe Val Val Val Leu Thr Gly Ile Leu Ala Thr Ala Gly
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        170                 175                 180

ACT GAC TTC GAC CTG CGA ACA CTG AGG GCT GTG CGT GTG CTG AGG CCC
688
Thr Asp Phe Asp Leu Arg Thr Leu Arg Ala Val Arg Val Leu Arg Pro
    185                 190                 195

CTG AAG CTG GTG TCT GGG ATT CCA AGT TTG CAG GTG GTG CTC AAG TCC
736
Leu Lys Leu Val Ser Gly Ile Pro Ser Leu Gln Val Val Leu Lys Ser
200                 205                 210                 215

ATC ATG AAG GCC ATG GTT CCA CTC CTG CAG ATT GGG CTG CTT CTC TTC
784
Ile Met Lys Ala Met Val Pro Leu Leu Gln Ile Gly Leu Leu Leu Phe
                220                 225                 230
TTT GCC ATC CTC ATG TTT GCC ATC ATT GGC CTG GAG TTC TAC ATG GGC
832
Phe Ala Ile Leu Met Phe Ala Ile Ile Gly Leu Glu Phe Tyr Met Gly
            235                 240                 245

AAG TTC CAC AAG GCC TGT TTC CCC AAC AGC ACA GAT GCG GAG CCC GTG
880
Lys Phe His Lys Ala Cys Phe Pro Asn Ser Thr Asp Ala Glu Pro Val
        250                 255                 260

GGT GAC TTC CCC TGT GGC AAG GAG GCC CCA GCC CGG CTG TGC GAG GGC
928
Gly Asp Phe Pro Cys Gly Lys Glu Ala Pro Ala Arg Leu Cys Glu Gly
    265                 270                 275

GAC ACT GAG TGC CGG GAG TAC TGG CCA GGA CCC AAC TTT GGC ATC ACC
976
Asp Thr Glu Cys Arg Glu Tyr Trp Pro Gly Pro Asn Phe Gly Ile Thr
280                 285                 290                 295

AAC TTT GAC AAT ATC CTG TTT GCC ATC TTG ACG GTG TTC CAG TGC ATC
1024
Asn Phe Asp Asn Ile Leu Phe Ala Ile Leu Thr Val Phe Gln Cys Ile
                300                 305                 310

ACC ATG GAG GGC TGG ACT GAC ATC CTC TAT AAT ACA AAC GAT GCG GCC
1072
Thr Met Glu Gly Trp Thr Asp Ile Leu Tyr Asn Thr Asn Asp Ala Ala
            315                 320                 325

GGC AAC ACC TGG AAC TGG CTC TAC TTC ATC CCT CTC ATC ATC ATC GGC
1120
Gly Asn Thr Trp Asn Trp Leu Tyr Phe Ile Pro Leu Ile Ile Ile Gly
        330                 335                 340

TCC TTC TTC ATG CTC AAC CTG GTG CTG GGC GTG CTC TCG GGG GAG TTT
1168
Ser Phe Phe Met Leu Asn Leu Val Leu Gly Val Leu Ser Gly Glu Phe
    345                 350                 355

GCC AAG GAG CGA GAG AGG GTG GAG AAC CGC CGC GCC TTC CTG AAG CTG
1216
Ala Lys Glu Arg Glu Arg Val Glu Asn Arg Arg Ala Phe Leu Lys Leu
360                 365                 370                 375
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CGC CGG CAG CAG CAG ATC GAG CGA GAG CTC AAC GGG TAC CTG GAG TGG
1264
Arg Arg Gln Gln Gln Ile Glu Arg Glu Leu Asn Gly Tyr Leu Glu Trp
                380                 385                 390

ATC TTC AAG GCG GAG GAA GTC ATG CTG GCC GAG GAG GAC AGG AAT GCA
1312
Ile Phe Lys Ala Glu Glu Val Met Leu Ala Glu Glu Asp Arg Asn Ala
            395                 400                 405

GAG GAG AAG TCC CCT TTG GAC GTG CTG AAG AGA GCG GCC ACC AAG AAG
1360
Glu Glu Lys Ser Pro Leu Asp Val Leu Lys Arg Ala Ala Thr Lys Lys
        410                 415                 420

AGC AGA AAT GAC CTG ATC CAC GCA GAG GAG GGA GAG GAC CGG TTT GCA
1408
Ser Arg Asn Asp Leu Ile His Ala Glu Glu Gly Glu Asp Arg Phe Ala
    425                 430                 435

GAT CTC TGT GCT GTT GGA TCC CCC TTC GCC CGC GCC AGC CTC AAG AGC
1456
Asp Leu Cys Ala Val Gly Ser Pro Phe Ala Arg Ala Ser Leu Lys Ser
440                 445                 450                 455

GGG AAG ACA GAG AGC TCG TCA TAC TTC CGG AGG AAG GAG AAG ATG TTC
1504
Gly Lys Thr Glu Ser Ser Ser Tyr Phe Arg Arg Lys Glu Lys Met Phe
                460                 465                 470

CGG TTT TTT ATC CGG CGC ATG GTG AAG GCT CAG AGC TTC TAC TGG GTG
1552
Arg Phe Phe Ile Arg Arg Met Val Lys Ala Gln Ser Phe Tyr Trp Val
            475                 480                 485

GTG CTG TGC GTG GTG GCC CTG AAC ACA CTG TGT GTG GCC ATG GTG CAT
1600
Val Leu Cys Val Val Ala Leu Asn Thr Leu Cys Val Ala Met Val His
        490                 495                 500

TAC AAC CAG CCG CGG CGG CTT ACC ACG ACC CTG TAT TTT GCA GAG TTT
1648
Tyr Asn Gln Pro Arg Arg Leu Thr Thr Thr Leu Tyr Phe Ala Glu Phe
    505                 510                 515

GTT TTC CTG GGT CTC TTC CTC ACA GAG ATG TCC CTG AAG ATG TAT GGC
1696
Val Phe Leu Gly Leu Phe Leu Thr Glu Met Ser Leu Lys Met Tyr Gly
520                 525                 530                 535

CTG GGG CCC AGA AGC TAC TTC CGG TCC TCC TTC AAC TGC TTC GAC TTT
1744
Leu Gly Pro Arg Ser Tyr Phe Arg Ser Ser Phe Asn Cys Phe Asp Phe
                540                 545                 550

GGG GTC ATC GTG GGG AGC GTC TTT GAA GTG GTC TGG GCG GCC ATC AAG
1792
Gly Val Ile Val Gly Ser Val Phe Glu Val Val Trp Ala Ala Ile Lys
            555                 560                 565

CCG GGA AGC TCC TTT GGG ATC AGT GTG CTG CGG GCC CTC CGC CTG CTG
1840
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Pro Gly Ser Ser Phe Gly Ile Ser Val Leu Arg Ala Leu Arg Leu Leu
        570                 575                 580

AGG ATC TTC AAA GTC ACG AAG TAC TGG AGC TCC CTG CGG AAC CTG GTG
1888
Arg Ile Phe Lys Val Thr Lys Tyr Trp Ser Ser Leu Arg Asn Leu Val
    585                 590                 595

GTG TCC CTG CTG AAC TCC ATG AAG TCC ATC ATC AGC CTG CTC TTC TTG
1936
Val Ser Leu Leu Asn Ser Met Lys Ser Ile Ile Ser Leu Leu Phe Leu
600                 605                 610                 615

CTC TTC CTG TTC ATT GTG GTC TTC GCC CTG CTG GGG ATG CAG CTG TTT
1984
Leu Phe Leu Phe Ile Val Val Phe Ala Leu Leu Gly Met Gln Leu Phe
                620                 625                 630

GGG GGA CAG TTC AAC TTC CAG GAT GAG ACT CCC ACA ACC AAC TTC GAC
2032
Gly Gly Gln Phe Asn Phe Gln Asp Glu Thr Pro Thr Thr Asn Phe Asp
            635                 640                 645

ACC TTC CCT GCC GCC ATC CTC ACT GTC TTC CAG ATC CTG ACG GGA GAG
2080
Thr Phe Pro Ala Ala Ile Leu Thr Val Phe Gln Ile Leu Thr Gly Glu
        650                 655                 660

GAC TGG AAT GCA GTG ATG TAT CAC GGG ATC GAA TCG CAA GGC GGC GTC
2128
Asp Trp Asn Ala Val Met Tyr His Gly Ile Glu Ser Gln Gly Gly Val
    665                 670                 675

AGC AAA GGC ATG TTC TCG TCC TTT TAC TTC ATT GTC CTG ACA CTG TTC
2176
Ser Lys Gly Met Phe Ser Ser Phe Tyr Phe Ile Val Leu Thr Leu Phe
680                 685                 690                 695

GGA AAC TAC ACT CTG CTG AAT GTC TTT CTG GCC ATC GCT GTG GAC AAC
2224
Gly Asn Tyr Thr Leu Leu Asn Val Phe Leu Ala Ile Ala Val Asp Asn
                700                 705                 710

CTG GCC AAC GCC CAA GAG CTG ACC AAG GAT GAA GAG GAG ATG GAA GAA
2272
Leu Ala Asn Ala Gln Glu Leu Thr Lys Asp Glu Glu Glu Met Glu Glu
            715                 720                 725

GCA GCC AAT CAG AAG CTT GCT CTG CAA AAG GCC AAA GAA GTG GCT GAA
2320
Ala Ala Asn Gln Lys Leu Ala Leu Gln Lys Ala Lys Glu Val Ala Glu
        730                 735                 740

GTC AGC CCC ATG TCT GCC GCG AAC ATC TCC ATC GCC GCC AGG CAG CAG
2368
Val Ser Pro Met Ser Ala Ala Asn Ile Ser Ile Ala Ala Arg Gln Gln
    745                 750                 755

AAC TCG GCC AAG GCG CGC TCG GTG TGG GAG CAG CGG GCC AGC CAG CTA
2416
Asn Ser Ala Lys Ala Arg Ser Val Trp Glu Gln Arg Ala Ser Gln Leu
760                 765                 770                 775
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CGG CTG CAG AAC CTG CGG GCC AGC TGC GAG GCG CTG TAC AGC GAG ATG
2464
Arg Leu Gln Asn Leu Arg Ala Ser Cys Glu Ala Leu Tyr Ser Glu Met
                780                 785                 790

GAC CCC GAG GAG CGG CTG CGC TTC GCC ACT ACG CGC CAC CGG CGG CCC
2512
Asp Pro Glu Glu Arg Leu Arg Phe Ala Thr Thr Arg His Arg Arg Pro
            795                 800                 805

GAC ATG AAG ACG CAC CTG GAC CGG CCG CTG GTG GTG GAG CTG GGC CGC
2560
Asp Met Lys Thr His Leu Asp Arg Pro Leu Val Val Glu Leu Gly Arg
        810                 815                 820

GAC GGC GCG CGG GGG CCC GTG GGA GGC AAA GCC CGA CCT GAG GCT GCG
2608
Asp Gly Ala Arg Gly Pro Val Gly Gly Lys Ala Arg Pro Glu Ala Ala
    825                 830                 835

GAG GCC CCC GAG GGC GTC GAC CCT CCG CGC AGG CAC CAC CGG CAC CGC
2656
Glu Ala Pro Glu Gly Val Asp Pro Pro Arg Arg His His Arg His Arg
840                 845                 850                 855

GAC AAG GAC AAG ACC CCC GCG GCG GGG GAC CAG GAC CGA GCA GAG GCC
2704
Asp Lys Asp Lys Thr Pro Ala Ala Gly Asp Gln Asp Arg Ala Glu Ala
                860                 865                 870

CCG AAG GCG GAG AGC GGG GAG CCC GGT GCC CGG GAG GAG CGG CCG CGG
2752
Pro Lys Ala Glu Ser Gly Glu Pro Gly Ala Arg Glu Glu Arg Pro Arg
            875                 880                 885

CCG CAC CGC AGC CAC AGC AAG GAG GCC GCG GGG CCC CCG GAG GCG CGG
2800
Pro His Arg Ser His Ser Lys Glu Ala Ala Gly Pro Pro Glu Ala Arg
        890                 895                 900

AGC GAG CGC GGC CGA GGC CCA GGC CCC GAG GGC GGC CGG CGG CAC CAC
2848
Ser Glu Arg Gly Arg Gly Pro Gly Pro Glu Gly Gly Arg Arg His His
    905                 910                 915

CGG CGC GGC TCC CCG GAG GAG GCG GCC GAG CGG GAG CCC CGA CGC CAC
2896
Arg Arg Gly Ser Pro Glu Glu Ala Ala Glu Arg Glu Pro Arg Arg His
920                 925                 930                 935

CGC GCG CAC CGG CAC CAG GAT CCG AGC AAG GAG TGC GCC GGC GCC AAG
2944
Arg Ala His Arg His Gln Asp Pro Ser Lys Glu Cys Ala Gly Ala Lys
                940                 945                 950

GGC GAG CGG CGC GCG CGG CAC CGC GGC GGC CCC CGA GCG GGG CCC CGG
2992
Gly Glu Arg Arg Ala Arg His Arg Gly Gly Pro Arg Ala Gly Pro Arg
            955                 960                 965
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GAG GCG GAG AGC GGG GAG GAG CCG GCG CGG CGG CAC CGG GCC CGG CAC
3040
Glu Ala Glu Ser Gly Glu Glu Pro Ala Arg Arg His Arg Ala Arg His
        970                 975                 980

AAG GCG CAG CCT GCT CAC GAG GCT GTG GAG AAG GAG ACC ACG GAG AAG
3088
Lys Ala Gln Pro Ala His Glu Ala Val Glu Lys Glu Thr Thr Glu Lys
    985                 990                 995

GAG GCC ACG GAG AAG GAG GCT GAG ATA GTG GAA GCC GAC AAG GAA AAG
3136
Glu Ala Thr Glu Lys Glu Ala Glu Ile Val Glu Ala Asp Lys Glu Lys
1000                1005                1010                1015

GAG CTC CGG AAC CAC CAG CCC CGG GAG CCA CAC TGT GAC CTG GAG ACC
3184
Glu Leu Arg Asn His Gln Pro Arg Glu Pro His Cys Asp Leu Glu Thr
                1020                1025                1030

AGT GGG ACT GTG ACT GTG GGT CCC ATG CAC ACA CTG CCC AGC ACC TGT
3232
Ser Gly Thr Val Thr Val Gly Pro Met His Thr Leu Pro Ser Thr Cys
            1035                1040                1045

CTC CAG AAG GTG GAG GAA CAG CCA GAG GAT GCA GAC AAT CAG CGG AAC
3280
Leu Gln Lys Val Glu Glu Gln Pro Glu Asp Ala Asp Asn Gln Arg Asn
        1050                1055                1060

GTC ACT CGC ATG GGC AGT CAG CCC CCA GAC CCG AAC ACT ATT GTA CAT
3328
Val Thr Arg Met Gly Ser Gln Pro Pro Asp Pro Asn Thr Ile Val His
    1065                1070                1075

ATC CCA GTG ATG CTG ACG GGC CCT CTT GGG GAA GCC ACG GTC GTT CCC
3376
Ile Pro Val Met Leu Thr Gly Pro Leu Gly Glu Ala Thr Val Val Pro
1080                1085                1090                1095

AGT GGT AAC GTG GAC CTG GAA AGC CAA GCA GAG GGG AAG AAG GAG GTG
3424
Ser Gly Asn Val Asp Leu Glu Ser Gln Ala Glu Gly Lys Lys Glu Val
                1100                1105                1110

GAA GCG GAT GAC GTG ATG AGG AGC GGC CCC CGG CCT ATC GTC CCA TAC
3472
Glu Ala Asp Asp Val Met Arg Ser Gly Pro Arg Pro Ile Val Pro Tyr
            1115                1120                1125

AGC TCC ATG TTC TGT TTA AGC CCC ACC AAC CTG CTC CGC CGC TTC TGC
3520
Ser Ser Met Phe Cys Leu Ser Pro Thr Asn Leu Leu Arg Arg Phe Cys
        1130                1135                1140

CAC TAC ATC GTG ACC ATG AGG TAC TTC GAG GTG GTC ATT CTC GTG GTC
3568
His Tyr Ile Val Thr Met Arg Tyr Phe Glu Val Val Ile Leu Val Val
    1145                1150                1155

ATC GCC TTG AGC AGC ATC GCC CTG GCT GCT GAG GAC CCA GTG CGC ACA
3616
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Ile Ala Leu Ser Ser Ile Ala Leu Ala Ala Glu Asp Pro Val Arg Thr
1160 1165 1170 1175

GAC TCG CCC AGG AAC AAC GCT CTG AAA TAC CTG GAT TAC ATT TTC ACT
3664
Asp Ser Pro Arg Asn Asn Ala Leu Lys Tyr Leu Asp Tyr Ile Phe Thr
1180 1185 1190

GGT GTC TTT ACC TTT GAG ATG GTG ATA AAG ATG ATC GAC TTG GGA CTG
3712
Gly Val Phe Thr Phe Glu Met Val Ile Lys Met Ile Asp Leu Gly Leu
1195 1200 1205

CTG CTT CAC CCT GGA GCC TAT TTC CGG GAC TTG TGG AAC ATT CTG GAC
3760
Leu Leu His Pro Gly Ala Tyr Phe Arg Asp Leu Trp Asn Ile Leu Asp
1210 1215 1220

TTC ATT GTG GTC AGT GGC GCC CTG GTG GCG TTT GCT TTC TCA GGA TCC
3808
Phe Ile Val Val Ser Gly Ala Leu Val Ala Phe Ala Phe Ser Gly Ser
1225 1230 1235

AAA GGG AAA GAC ATC AAT ACC ATC AAG TCT CTG AGA GTC CTT CGT GTC
3856
Lys Gly Lys Asp Ile Asn Thr Ile Lys Ser Leu Arg Val Leu Arg Val
1240 1245 1250 1255

CTG CGG CCC CTC AAG ACC ATC AAA CGG CTG CCC AAG CTC AAG GCT GTG
3904
Leu Arg Pro Leu Lys Thr Ile Lys Arg Leu Pro Lys Leu Lys Ala Val
1260 1265 1270

TTT GAC TGT GTG GTG AAC TCC CTG AAG AAT GTC CTC AAC ATC TTG ATT
3952
Phe Asp Cys Val Val Asn Ser Leu Lys Asn Val Leu Asn Ile Leu Ile
1275 1280 1285

GTC TAC ATG CTC TTC ATG TTC ATA TTT GCC GTC ATT GCG GTG CAG CTC
4000
Val Tyr Met Leu Phe Met Phe Ile Phe Ala Val Ile Ala Val Gln Leu
1290 1295 1300

TTC AAA GGG AAG TTT TTC TAC TGC ACA GAT GAA TCC AAG GAG CTG GAG
4048
Phe Lys Gly Lys Phe Phe Tyr Cys Thr Asp Glu Ser Lys Glu Leu Glu
1305 1310 1315

AGG GAC TGC AGG GGT CAG TAT TTG GAT TAT GAG AAG GAG GAA GTG GAA
4096
Arg Asp Cys Arg Gly Gln Tyr Leu Asp Tyr Glu Lys Glu Glu Val Glu
1320 1325 1330 1335

GCT CAG CCC AGG CAG TGG AAG AAA TAC GAC TTT CAC TAC GAC AAT GTG
4144
Ala Gln Pro Arg Gln Trp Lys Lys Tyr Asp Phe His Tyr Asp Asn Val
1340 1345 1350

CTC TGG GCT CTG CTG ACG CTG TTC ACA GTG TCC ACG GGA GAA GGC TGG
4192
Leu Trp Ala Leu Leu Thr Leu Phe Thr Val Ser Thr Gly Glu Gly Trp
1355 1360 1365

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CCC ATG GTG CTG AAA CAC TCC GTG GAT GCC ACC TAT GAG GAG CAG GGT
4240
Pro Met Val Leu Lys His Ser Val Asp Ala Thr Tyr Glu Glu Gln Gly
        1370                1375                1380

CCA AGC CCT GGG TAC CGC ATG GAG CTG TCC ATC TTC TAC GTG GTC TAC
4288
Pro Ser Pro Gly Tyr Arg Met Glu Leu Ser Ile Phe Tyr Val Val Tyr
    1385                1390                1395

TTT GTG GTC TTT CCC TTC TTC TTC GTC AAC ATC TTT GTG GCT TTG ATC
4336
Phe Val Val Phe Pro Phe Phe Phe Val Asn Ile Phe Val Ala Leu Ile
1400                1405                1410                1415

ATC ATC ACC TTC CAG GAG CAG GGG GAC AAG GTG ATG TCT GAA TGC AGC
4384
Ile Ile Thr Phe Gln Glu Gln Gly Asp Lys Val Met Ser Glu Cys Ser
                1420                1425                1430

CTG GAG AAG AAC GAG AGG GCT TGC ATT GAC TTC GCC ATC AGC GCC AAA
4432
Leu Glu Lys Asn Glu Arg Ala Cys Ile Asp Phe Ala Ile Ser Ala Lys
            1435                1440                1445

CCC CTG ACA CGG TAC ATG CCC CAA AAC CGG CAG TCG TTC CAG TAT AAG
4480
Pro Leu Thr Arg Tyr Met Pro Gln Asn Arg Gln Ser Phe Gln Tyr Lys
        1450                1455                1460

ACG TGG ACA TTT GTG GTC TCC CCG CCC TTT GAA TAC TTC ATC ATG GCC
4528
Thr Trp Thr Phe Val Val Ser Pro Pro Phe Glu Tyr Phe Ile Met Ala
    1465                1470                1475

ATG ATA GCC CTC AAC ACT GTG GTG CTG ATG ATG AAG TTC TAT GAT GCA
4576
Met Ile Ala Leu Asn Thr Val Val Leu Met Met Lys Phe Tyr Asp Ala
1480                1485                1490                1495

CCC TAT GAG TAC GAG CTG ATG CTG AAA TGC CTG AAC ATC GTG TTC ACA
4624
Pro Tyr Glu Tyr Glu Leu Met Leu Lys Cys Leu Asn Ile Val Phe Thr
                1500                1505                1510

TCC ATG TTC TCC ATG GAA TGC GTG CTG A G ATC ATC GCC TTT GGG GTG
4672
Ser Met Phe Ser Met Glu Cys Val Leu Lys Ile Ile Ala Phe Gly Val
            1515                1520                1525

CTG AAC TAT TTC AGA GAT GCC TGG AAT GTC TTT GAC TTT GTC ACT GTG
4720
Leu Asn Tyr Phe Arg Asp Ala Trp Asn Val Phe Asp Phe Val Thr Val
        1530                1535                1540

TTG GGA AGT ATT ACT GAT ATT TTA GTA ACA GAG ATT GCG AAC AAT TTC
4768
Leu Gly Ser Ile Thr Asp Ile Leu Val Thr Glu Ile Ala Asn Asn Phe
    1545                1550                1555
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ATC AAC CTC AGC TTC CTC CGC CTC TTT CGA GCT GCG CGG CTG ATC AAG
4816
Ile Asn Leu Ser Phe Leu Arg Leu Phe Arg Ala Ala Arg Leu Ile Lys
1560                1565                1570                1575

CTG CTC CGC CAG GGC TAC ACC ATC CGC ATC CTG CTG TGG ACC TTT GTC
4864
Leu Leu Arg Gln Gly Tyr Thr Ile Arg Ile Leu Leu Trp Thr Phe Val
                1580                1585                1590

CAG TCC TTC AAG GCC CTG CCC TAC GTG TGT CTG CTC ATT GCC ATG CTG
4912
Gln Ser Phe Lys Ala Leu Pro Tyr Val Cys Leu Leu Ile Ala Met Leu
            1595                1600                1605

TTC TTC ATC TAC GCC ATC ATC GGC ATG CAG GTG TTT GGG AAT ATT GCC
4960
Phe Phe Ile Tyr Ala Ile Ile Gly Met Gln Val Phe Gly Asn Ile Ala
        1610                1615                1620

CTG GAT GAT GAC ACC AGC ATC AAC CGC CAC AAC AAC TTC CGG ACG TTT
5008
Leu Asp Asp Asp Thr Ser Ile Asn Arg His Asn Asn Phe Arg Thr Phe
    1625                1630                1635

TTG CAA GCC CTG ATG CTG CTG TTC AGG AGC GCC ACG GGG GAG GCC TGG
5056
Leu Gln Ala Leu Met Leu Leu Phe Arg Ser Ala Thr Gly Glu Ala Trp
1640                1645                1650                1655

CAC GAG ATC ATG CTG TCC TGC CTG AGC AAC CAG GCC TGT GAT GAG CAG
5104
His Glu Ile Met Leu Ser Cys Leu Ser Asn Gln Ala Cys Asp Glu Gln
                1660                1665                1670

GCC AAT GCC ACC GAG TGT GGA AGT GAC TTT GCC TAC TTC TAC TTC GTC
5152
Ala Asn Ala Thr Glu Cys Gly Ser Asp Phe Ala Tyr Phe Tyr Phe Val
            1675                1680                1685

TCC TTC ATC TTC CTG TGC TCC TTT CTG ATG TTG AAC CTC TTT GTG GCT
5200
Ser Phe Ile Phe Leu Cys Ser Phe Leu Met Leu Asn Leu Phe Val Ala
        1690                1695                1700

GTG ATC ATG GAC AAT TTT GAG TAC CTC ACG CGG GAC TCT TCC ATC CTA
5248
Val Ile Met Asp Asn Phe Glu Tyr Leu Thr Arg Asp Ser Ser Ile Leu
    1705                1710                1715

GGT CCT CAC CAC TTG GAT GAG TTC ATC CGG GTC TGG GCT GAA TAC GAC
5296
Gly Pro His His Leu Asp Glu Phe Ile Arg Val Trp Ala Glu Tyr Asp
1720                1725                1730                1735

CCG GCT GCG TGT GGG CGC ATC AGT TAC AAT GAC ATG TTT GAG ATG CTG
5344
Pro Ala Ala Cys Gly Arg Ile Ser Tyr Asn Asp Met Phe Glu Met Leu
                1740                1745                1750

AAA CAC ATG TCC CCG CCT CTG GGG CTG GGG AAG AAA TGC CCT GCT CGA
5392
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Lys His Met Ser Pro Pro Leu Gly Leu Gly Lys Lys Cys Pro Ala Arg
            1755                1760                1765

GTT GCT TAC AAG CGC CTG GTT CGC ATG AAC ATG CCC ATC TCC AAC GAG
5440
Val Ala Tyr Lys Arg Leu Val Arg Met Asn Met Pro Ile Ser Asn Glu
        1770                1775                1780

GAC ATG ACT GTT CAC TTC ACG TCC ACG CTG ATG GCC CTC ATC CGG ACG
5488
Asp Met Thr Val His Phe Thr Ser Thr Leu Met Ala Leu Ile Arg Thr
    1785                1790                1795

GCA CTG GAG ATC AAG CTG GCC CCA GCT GGG ACA AAG CAG CAT CAG TGT
5536
Ala Leu Glu Ile Lys Leu Ala Pro Ala Gly Thr Lys Gln His Gln Cys
1800                1805                1810                1815

GAC GCG GAG TTG AGG AAG GAG ATT TCC GTT GTG TGG GCC AAT CTG CCC
5584
Asp Ala Glu Leu Arg Lys Glu Ile Ser Val Val Trp Ala Asn Leu Pro
                1820                1825                1830

CAG AAG ACT TTG GAC TTG CTG GTA CCA CCC CAT AAG CCT GAT GAG ATG
5632
Gln Lys Thr Leu Asp Leu Leu Val Pro Pro His Lys Pro Asp Glu Met
            1835                1840                1845

ACA GTG GGG AAG GTT TAT GCA GCT CTG ATG ATA TTT GAC TTC TAC AAG
5680
Thr Val Gly Lys Val Tyr Ala Ala Leu Met Ile Phe Asp Phe Tyr Lys
        1850                1855                1860

CAG AAC AAA ACC ACC AGA GAC CAG ATG CAG CAG GCT CCT GGA GGC CTC
5728
Gln Asn Lys Thr Thr Arg Asp Gln Met Gln Gln Ala Pro Gly Gly Leu
    1865                1870                1875

TCC CAG ATG GGT CCT GTG TCC CTG TTC CAC CCT CTG AAG GCC ACC CTG
5776
Ser Gln Met Gly Pro Val Ser Leu Phe His Pro Leu Lys Ala Thr Leu
1880                1885                1890                1895

GAG CAG ACA CAG CCG GCT GTG CTC CGA GGA GCC CGG GTT TTC CTT CGA
5824
Glu Gln Thr Gln Pro Ala Val Leu Arg Gly Ala Arg Val Phe Leu Arg
                1900                1905                1910

CAG AAG AGT TCC ACC TCC CTC AGC AAT GGC GGG GCC ATA CAA AAC CAA
5872
Gln Lys Ser Ser Thr Ser Leu Ser Asn Gly Gly Ala Ile Gln Asn Gln
            1915                1920                1925

GAG AGT GGC ATC AAA GAG TCT GTC TCC TGG GGC ACT CAA AGG ACC CAG
5920
Glu Ser Gly Ile Lys Glu Ser Val Ser Trp Gly Thr Gln Arg Thr Gln
        1930                1935                1940

GAT GCA CCC CAT GAG GCC AGG CCA CCC CTG GAG CGT GGC CAC TCC ACA
5968
Asp Ala Pro His Glu Ala Arg Pro Pro Leu Glu Arg Gly His Ser Thr
    1945                1950                1955
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GAG ATC CCT GTG GGG CGG TCA GGA GCA CTG GCT GTG GAC GTT CAG ATG
6016
Glu Ile Pro Val Gly Arg Ser Gly Ala Leu Ala Val Asp Val Gln Met
1960                1965                1970                1975

CAG AGC ATA ACC CGG AGG GGC CCT GAT GGG GAG CCC CAG CCT GGG CTG
6064
Gln Ser Ile Thr Arg Arg Gly Pro Asp Gly Glu Pro Gln Pro Gly Leu
                1980                1985                1990

GAG AGC CAG GGT CGA GCG GCC TCC ATG CCC CGC CTT GCG GCC GAG ACT
6112
Glu Ser Gln Gly Arg Ala Ala Ser Met Pro Arg Leu Ala Ala Glu Thr
            1995                2000                2005

CAG CCC GTC ACA GAT GCC AGC CCC ATG AAG CGC TCC ATC TCC ACG CTG
6160
Gln Pro Val Thr Asp Ala Ser Pro Met Lys Arg Ser Ile Ser Thr Leu
        2010                2015                2020

GCC CAG CGG CCC CGT GGG ACT CAT CTT TGC AGC ACC ACC CCG GAC CGC
6208
Ala Gln Arg Pro Arg Gly Thr His Leu Cys Ser Thr Thr Pro Asp Arg
    2025                2030                2035

CCA CCC CCT AGC CAG GCG TCG TCG CAC CAC CAC CAC CAC CGC TGC CAC
6256
Pro Pro Pro Ser Gln Ala Ser Ser His His His His His Arg Cys His
2040                2045                2050                2055

CGC CGC AGG GAC AGG AAG CAG AGG TCC CTG GAG AAG GGG CCC AGC CTG
6304
Arg Arg Arg Asp Arg Lys Gln Arg Ser Leu Glu Lys Gly Pro Ser Leu
                2060                2065                2070

TCT GCC GAT ATG GAT GGC GCA CCA AGC AGT GCT GTG GGG CCG GGG CTG
6352
Ser Ala Asp Met Asp Gly Ala Pro Ser Ser Ala Val Gly Pro Gly Leu
            2075                2080                2085

CCC CCG GGA GAG GGG CCT ACA GGC TGC CGG CGG GAA CGA GAG CGC CGG
6400
Pro Pro Gly Glu Gly Pro Thr Gly Cys Arg Arg Glu Arg Glu Arg Arg
        2090                2095                2100

CAG GAG CGG AGC CGG TCC CAG GAG CGG AGG CAG CCC TCA TCC TCC TCC
6448
Gln Glu Arg Ser Arg Ser Gln Glu Arg Arg Gln Pro Ser Ser Ser Ser
    2105                2110                2115

TCG GAG AAG CAG CGC TTC TAC TCC TGC GAC CGC TTT GGG GGC CGT GAG
6496
Ser Glu Lys Gln Arg Phe Tyr Ser Cys Asp Arg Phe Gly Gly Arg Glu
2120                2125                2130                2135

CCC CCG AAG CCC AAG CCC TCC CTC AGC AGC CAC CCA ACG TCG CCA ACA
6544
Pro Pro Lys Pro Lys Pro Ser Leu Ser Ser His Pro Thr Ser Pro Thr
                2140                2145                2150
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GCT GGC CAG GAG CCG GGA CCC CAC CCA CAG GGC AGT GGT TCC GTG AAT
6592
Ala Gly Gln Glu Pro Gly Pro His Pro Gln Gly Ser Gly Ser Val Asn
          2155                2160                2165

GGG AGC CCC TTG CTG TCA ACA TCT GGT GCT AGC ACC CCC GGC CGC GGT
6640
Gly Ser Pro Leu Leu Ser Thr Ser Gly Ala Ser Thr Pro Gly Arg Gly
      2170                2175                2180

GGG CGG AGG CAG CTC CCC CAG ACG CCC CTG ACT CCC CGC CCC AGC ATC
6688
Gly Arg Arg Gln Leu Pro Gln Thr Pro Leu Thr Pro Arg Pro Ser Ile
  2185                2190                2195

ACC TAC AAG ACG GCC AAC TCC TCA CCC ATC CAC TTC GCC GGG GCT CAG
6736
Thr Tyr Lys Thr Ala Asn Ser Ser Pro Ile His Phe Ala Gly Ala Gln
2200                2205                2210                2215

ACC AGC CTC CCT GCC TTC TCC CCA GGC CGG CTC AGC CGT GGG CTT TCC
6784
Thr Ser Leu Pro Ala Phe Ser Pro Gly Arg Leu Ser Arg Gly Leu Ser
                2220                2225                2230

GAA CAC AAC GCC CTG CTG CAG AGA GAC CCC CTC AGC CAG CCC CTG GCC
6832
Glu His Asn Ala Leu Leu Gln Arg Asp Pro Leu Ser Gln Pro Leu Ala
          2235                2240                2245

CCT GGC TCT CGA ATT GGC TCT GAC CCT TAC CTG GGG CAG CGT CTG GAC
6880
Pro Gly Ser Arg Ile Gly Ser Asp Pro Tyr Leu Gly Gln Arg Leu Asp
      2250                2255                2260

AGT GAG GCC TCT GTC CAC GCC CTG CCT GAG GAC ACG CTC ACT TTC GAG
6928
Ser Glu Ala Ser Val His Ala Leu Pro Glu Asp Thr Leu Thr Phe Glu
  2265                2270                2275

GAG GCT GTG GCC ACC AAC TCG GGC CGC TCC TCC AGG ACT TCC TAC GTG
6976
Glu Ala Val Ala Thr Asn Ser Gly Arg Ser Ser Arg Thr Ser Tyr Val
2280                2285                2290                2295

TCC TCC CTG ACC TCC CAG TCT CAC CCT CTC CGC CGC GTG CCC AAC GGT
7024
Ser Ser Leu Thr Ser Gln Ser His Pro Leu Arg Arg Val Pro Asn Gly
                2300                2305                2310

TAC CAC TGC ACC CTG GGA CTC AGC TCG GGT GGC CGA GCA CGG CAC AGC
7072
Tyr His Cys Thr Leu Gly Leu Ser Ser Gly Gly Arg Ala Arg His Ser
          2315                2320                2325

TAC CAC CAC CCT GAC CAA GAC CAC TGG TGC TAGCTGCACC GTGACCGCTC
7122
Tyr His His Pro Asp Gln Asp His Trp Cys
      2330                2335

AGACGCCTGC ATGCAGCAGG CGTGTGTTCC AGTGGATGAG TTTTATCATC CACACGGGGC
7182
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AGTCGGCCCT CGGGGGAGGC CTTGCCCACC TTGGTGAGGC TCCTGTGGCC CCTCCCTCCC
7242

CCTCCTCCCC TCTTTTACTC TAGA
7266

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2337 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Val Arg Phe Gly Asp Glu Leu Gly Gly Arg Tyr Gly Gly Pro Gly
1 5 10 15

Ser Gly Glu Arg Ala Arg Gly Gly Gly Ala Gly Gly Ala Gly Gly Pro
20 25 30

Gly Pro Gly Gly Leu Gln Pro Gly Gln Arg Val Leu Tyr Lys Gln Ser
35 40 45

Ile Ala Gln Arg Ala Arg Thr Met Ala Leu Tyr Asn Pro Ile Pro Val
50 55 60

Lys Gln Asn Cys Phe Thr Val Asn Arg Ser Leu Phe Val Phe Ser Glu
65 70 75 80

Asp Asn Val Val Arg Lys Tyr Ala Lys Arg Ile Thr Glu Trp Pro Pro
85 90 95

Phe Glu Tyr Met Ile Leu Ala Thr Ile Ile Ala Asn Cys Ile Val Leu
100 105 110

Ala Leu Glu Gln His Leu Pro Asp Gly Asp Lys Thr Pro Met Ser Glu
115 120 125

Arg Leu Asp Asp Thr Glu Pro Tyr Phe Ile Gly Ile Phe Cys Phe Glu
130 135 140

Ala Gly Ile Lys Ile Ile Ala Leu Gly Phe Val Phe His Lys Gly Ser
145 150 155 160

Tyr Leu Arg Asn Gly Trp Asn Val Met Asp Phe Val Val Val Leu Thr
165 170 175

Gly Ile Leu Ala Thr Ala Gly Thr Asp Phe Asp Leu Arg Thr Leu Arg
180 185 190

Ala Val Arg Val Leu Arg Pro Leu Lys Leu Val Ser Gly Ile Pro Ser
195 200 205

Leu Gln Val Val Leu Lys Ser Ile Met Lys Ala Met Val Pro Leu Leu
210 215 220

Gln Ile Gly Leu Leu Leu Ph Phe Ala Ile L u M t Phe Ala Ile Ile
225 230 235 240

Gly Leu Glu Phe Tyr Met Gly Lys Phe His Lys Ala Cys Phe Pro Asn
245 250 255

Ser Thr Asp Ala Glu Pro Val Gly Asp Phe Pro Cys Gly Lys Glu Ala
260 265 270

Pro Ala Arg Leu Cys Glu Gly Asp Thr Glu Cys Arg Glu Tyr Trp Pro
275 280 285

Gly Pro Asn Phe Gly Ile Thr Asn Phe Asp Asn Ile Leu Phe Ala Ile
290 295 300

Leu Thr Val Phe Gln Cys Ile Thr Met Glu Gly Trp Thr Asp Ile Leu
305 310 315 320

Tyr Asn Thr Asn Asp Ala Ala Gly Asn Thr Trp Asn Trp Leu Tyr Phe
325 330 335

Ile Pro Leu Ile Ile Ile Gly Ser Phe Phe Met Leu Asn Leu Val Leu
340 345 350

Gly Val Leu Ser Gly Glu Phe Ala Lys Glu Arg Glu Arg Val Glu Asn
355 360 365

Arg Arg Ala Phe Leu Lys Leu Arg Arg Gln Gln Gln Ile Glu Arg Glu
370 375 380

Leu Asn Gly Tyr Leu Glu Trp Ile Phe Lys Ala Glu Glu Val Met Leu
385 390 395 400

Ala Glu Glu Asp Arg Asn Ala Glu Glu Lys Ser Pro Leu Asp Val Leu
405 410 415

Lys Arg Ala Ala Thr Lys Lys Ser Arg Asn Asp Leu Ile His Ala Glu
420 425 430

Glu Gly Glu Asp Arg Phe Ala Asp Leu Cys Ala Val Gly Ser Pro Phe
435 440 445

Ala Arg Ala Ser Leu Lys Ser Gly Lys Thr Glu Ser Ser Ser Tyr Phe
450 455 460

Arg Arg Lys Glu Lys Met Phe Arg Phe Phe Ile Arg Arg Met Val Lys
465 470 475 480

Ala Gln Ser Phe Tyr Trp Val Val Leu Cys Val Val Ala Leu Asn Thr
485 490 495

Leu Cys Val Ala Met Val His Tyr Asn Gln Pro Arg Arg Leu Thr Thr
500 505 510

Thr Leu Tyr Phe Ala Glu Phe Val Phe Leu Gly Leu Phe Leu Thr Glu
515 520 525

Met Ser Leu Lys Met Tyr Gly Leu Gly Pro Arg Ser Tyr Phe Arg Ser
530 535 540

Ser Phe Asn Cys Phe Asp Phe Gly Val Ile Val Gly Ser Val Phe Glu
545 550 555 560

Val Val Trp Ala Ala Ile Lys Pro Gly Ser Ser Phe Gly Ile Ser Val

565 570 575

Leu Arg Ala Leu Arg Leu Leu Arg Ile Phe Lys Val Thr Lys Tyr Trp
580 585 590

Ser Ser Leu Arg Asn Leu Val Val Ser Leu Leu Asn Ser Met Lys Ser
595 600 605

Ile Ile Ser Leu Leu Phe Leu Leu Phe Leu Phe Ile Val Val Phe Ala
610 615 620

Leu Leu Gly Met Gln Leu Phe Gly Gly Gln Phe Asn Phe Gln Asp Glu
625 630 635 640

Thr Pro Thr Thr Asn Phe Asp Thr Phe Pro Ala Ala Ile Leu Thr Val
645 650 655

Phe Gln Ile Leu Thr Gly Glu Asp Trp Asn Ala Val Met Tyr His Gly
660 665 670

Ile Glu Ser Gln Gly Gly Val Ser Lys Gly Met Phe Ser Ser Phe Tyr
675 680 685

Phe Ile Val Leu Thr Leu Phe Gly Asn Tyr Thr Leu Leu Asn Val Phe
690 695 700

Leu Ala Ile Ala Val Asp Asn Leu Ala Asn Ala Gln Glu Leu Thr Lys
705 710 715 720

Asp Glu Glu Glu Met Glu Glu Ala Ala Asn Gln Lys Leu Ala Leu Gln
725 730 735

Lys Ala Lys Glu Val Ala Glu Val Ser Pro Met Ser Ala Ala Asn Ile
740 745 750

Ser Ile Ala Ala Arg Gln Gln Asn Ser Ala Lys Ala Arg Ser Val Trp
755 760 765

Glu Gln Arg Ala Ser Gln Leu Arg Leu Gln Asn Leu Arg Ala Ser Cys
770 775 780

Glu Ala Leu Tyr Ser Glu Met Asp Pro Glu Glu Arg Leu Arg Phe Ala
785 790 795 800

Thr Thr Arg His Arg Arg Pro Asp Met Lys Thr His Leu Asp Arg Pro
805 810 815

Leu Val Val Glu Leu Gly Arg Asp Gly Ala Arg Gly Pro Val Gly Gly
820 825 830

Lys Ala Arg Pro Glu Ala Ala Glu Ala Pro Glu Gly Val Asp Pro Pro
835 840 845

Arg Arg His His Arg His Arg Asp Lys Asp Lys Thr Pro Ala Ala Gly
850 855 860

Asp Gln Asp Arg Ala Glu Ala Pro Lys Ala Glu Ser Gly Glu Pro Gly
865 870 875 880

Ala Arg Glu Glu Arg Pro Arg Pro His Arg Ser His Ser Lys Glu Ala
885 890 895

Ala Gly Pro Pro Glu Ala Arg Ser Glu Arg Gly Arg Gly Pro Gly Pro

900 905 910

Glu Gly Gly Arg Arg His His Arg Arg Gly Ser Pro Glu Glu Ala Ala
915 920 925

Glu Arg Glu Pro Arg Arg His Arg Ala His Arg His Gln Asp Pro Ser
930 935 940

Lys Glu Cys Ala Gly Ala Lys Gly Glu Arg Arg Ala Arg His Arg Gly
945 950 955 960

Gly Pro Arg Ala Gly Pro Arg Glu Ala Glu Ser Gly Glu Glu Pro Ala
965 970 975

Arg Arg His Arg Ala Arg His Lys Ala Gln Pro Ala His Glu Ala Val
980 985 990

Glu Lys Glu Thr Thr Glu Lys Glu Ala Thr Glu Lys Glu Ala Glu Ile
995 1000 1005

Val Glu Ala Asp Lys Glu Lys Glu Leu Arg Asn His Gln Pro Arg Glu
1010 1015 1020

Pro His Cys Asp Leu Glu Thr Ser Gly Thr Val Thr Val Gly Pro Met
1025 1030 1035 1040

His Thr Leu Pro Ser Thr Cys Leu Gln Lys Val Glu Glu Gln Pro Glu
1045 1050 1055

Asp Ala Asp Asn Gln Arg Asn Val Thr Arg Met Gly Ser Gln Pro Pro
1060 1065 1070

Asp Pro Asn Thr Ile Val His Ile Pro Val Met Leu Thr Gly Pro Leu
1075 1080 1085

Gly Glu Ala Thr Val Val Pro Ser Gly Asn Val Asp Leu Glu Ser Gln
1090 1095 1100

Ala Glu Gly Lys Lys Glu Val Glu Ala Asp Asp Val Met Arg Ser Gly
1105 1110 1115 1120

Pro Arg Pro Ile Val Pro Tyr Ser Ser Met Phe Cys Leu Ser Pro Thr
1125 1130 1135

Asn Leu Leu Arg Arg Phe Cys His Tyr Ile Val Thr Met Arg Tyr Phe
1140 1145 1150

Glu Val Val Ile Leu Val Val Ile Ala Leu Ser Ser Ile Ala Leu Ala
1155 1160 1165

Ala Glu Asp Pro Val Arg Thr Asp Ser Pro Arg Asn Asn Ala Leu Lys
1170 1175 1180

Tyr Leu Asp Tyr Ile Phe Thr Gly Val Phe Thr Phe Glu Met Val Ile
1185 1190 1195 1200

Lys Met Ile Asp Leu Gly Leu Leu Leu His Pro Gly Ala Tyr Phe Arg
1205 1210 1215

Asp Leu Trp Asn Ile Leu Asp Phe Ile Val Val Ser Gly Ala Leu Val
1220 1225 1230

Ala Phe Ala Phe Ser Gly Ser Lys Gly Lys Asp Ile Asn Thr Ile Lys

1235 1240 1245

Ser Leu Arg Val Leu Arg Val Leu Arg Pro Leu Lys Thr Ile Lys Arg
1250 1255 1260

Leu Pro Lys Leu Lys Ala Val Phe Asp Cys Val Val Asn Ser Leu Lys
1265 1270 1275 1280

Asn Val Leu Asn Ile Leu Ile Val Tyr Met Leu Phe Met Phe Ile Phe
1285 1290 1295

Ala Val Ile Ala Val Gln Leu Phe Lys Gly Lys Phe Phe Tyr Cys Thr
1300 1305 1310

Asp Glu Ser Lys Glu Leu Glu Arg Asp Cys Arg Gly Gln Tyr Leu Asp
1315 1320 1325

Tyr Glu Lys Glu Glu Val Glu Ala Gln Pro Arg Gln Trp Lys Lys Tyr
1330 1335 1340

Asp Phe His Tyr Asp Asn Val Leu Trp Ala Leu Leu Thr Leu Phe Thr
1345 1350 1355 1360

Val Ser Thr Gly Glu Gly Trp Pro Met Val Leu Lys His Ser Val Asp
1365 1370 1375

Ala Thr Tyr Glu Glu Gln Gly Pro Ser Pro Gly Tyr Arg Met Glu Leu
1380 1385 1390

Ser Ile Phe Tyr Val Val Tyr Phe Val Val Phe Pro Phe Phe Phe Val
1395 1400 1405

Asn Ile Phe Val Ala Leu Ile Ile Ile Thr Phe Gln Glu Gln Gly Asp
1410 1415 1420

Lys Val Met Ser Glu Cys Ser Leu Glu Lys Asn Glu Arg Ala Cys Ile
1425 1430 1435 1440

Asp Phe Ala Ile Ser Ala Lys Pro Leu Thr Arg Tyr Met Pro Gln Asn
1445 1450 1455

Arg Gln Ser Phe Gln Tyr Lys Thr Trp Thr Phe Val Val Ser Pro Pro
1460 1465 1470

Phe Glu Tyr Phe Ile Met Ala Met Ile Ala Leu Asn Thr Val Val Leu
1475 1480 1485

Met Met Lys Phe Tyr Asp Ala Pro Tyr Glu Tyr Glu Leu Met Leu Lys
1490 1495 1500

Cys Leu Asn Ile Val Phe Thr Ser Met Phe Ser Met Glu Cys Val Leu
1505 1510 1515 1520

Lys Ile Ile Ala Phe Gly Val Leu Asn Tyr Phe Arg Asp Ala Trp Asn
1525 1530 1535

Val Phe Asp Phe Val Thr Val Leu Gly Ser Ile Thr Asp Ile Leu Val
1540 1545 1550

Thr Glu Il Ala Asn Asn Phe Ile Asn Leu Ser Phe L u Arg Leu Phe
1555 1560 1565

Arg Ala Ala Arg Leu Ile Lys Leu Leu Arg Gln Gly Tyr Thr Ile Arg

1570 1575 1580

Ile Leu Leu Trp Thr Phe Val Gln Ser Phe Lys Ala Leu Pro Tyr Val
1585 1590 1595 1600

Cys Leu Leu Ile Ala Met Leu Phe Phe Ile Tyr Ala Ile Ile Gly Met
1605 1610 1615

Gln Val Phe Gly Asn Ile Ala Leu Asp Asp Asp Thr Ser Ile Asn Arg
1620 1625 1630

His Asn Asn Phe Arg Thr Phe Leu Gln Ala Leu Met Leu Leu Phe Arg
1635 1640 1645

Ser Ala Thr Gly Glu Ala Trp His Glu Ile Met Leu Ser Cys Leu Ser
1650 1655 1660

Asn Gln Ala Cys Asp Glu Gln Ala Asn Ala Thr Glu Cys Gly Ser Asp
1665 1670 1675 1680

Phe Ala Tyr Phe Tyr Phe Val Ser Phe Ile Phe Leu Cys Ser Phe Leu
1685 1690 1695

Met Leu Asn Leu Phe Val Ala Val Ile Met Asp Asn Phe Glu Tyr Leu
1700 1705 1710

Thr Arg Asp Ser Ser Ile Leu Gly Pro His His Leu Asp Glu Phe Ile
1715 1720 1725

Arg Val Trp Ala Glu Tyr Asp Pro Ala Ala Cys Gly Arg Ile Ser Tyr
1730 1735 1740

Asn Asp Met Phe Glu Met Leu Lys His Met Ser Pro Pro Leu Gly Leu
1745 1750 1755 1760

Gly Lys Lys Cys Pro Ala Arg Val Ala Tyr Lys Arg Leu Val Arg Met
1765 1770 1775

Asn Met Pro Ile Ser Asn Glu Asp Met Thr Val His Phe Thr Ser Thr
1780 1785 1790

Leu Met Ala Leu Ile Arg Thr Ala Leu Glu Ile Lys Leu Ala Pro Ala
1795 1800 1805

Gly Thr Lys Gln His Gln Cys Asp Ala Glu Leu Arg Lys Glu Ile Ser
1810 1815 1820

Val Val Trp Ala Asn Leu Pro Gln Lys Thr Leu Asp Leu Leu Val Pro
1825 1830 1835 1840

Pro His Lys Pro Asp Glu Met Thr Val Gly Lys Val Tyr Ala Ala Leu
1845 1850 1855

Met Ile Phe Asp Phe Tyr Lys Gln Asn Lys Thr Thr Arg Asp Gln Met
1860 1865 1870

Gln Gln Ala Pro Gly Gly Leu Ser Gln Met Gly Pro Val Ser Leu Phe
1875 1880 1885

His Pro Leu Lys Ala Thr Leu Glu Gln Thr Gln Pro Ala Val Leu Arg
1890 1895 1900

Gly Ala Arg Val Phe Leu Arg Gln Lys Ser Ser Thr Ser Leu Ser Asn

1905 1910 1915 1920

Gly Gly Ala Ile Gln Asn Gln Glu Ser Gly Ile Lys Glu Ser Val Ser
1925 1930 1935

Trp Gly Thr Gln Arg Thr Gln Asp Ala Pro His Glu Ala Arg Pro Pro
1940 1945 1950

Leu Glu Arg Gly His Ser Thr Glu Ile Pro Val Gly Arg Ser Gly Ala
1955 1960 1965

Leu Ala Val Asp Val Gln Met Gln Ser Ile Thr Arg Arg Gly Pro Asp
1970 1975 1980

Gly Glu Pro Gln Pro Gly Leu Glu Ser Gln Gly Arg Ala Ala Ser Met
1985 1990 1995 2000

Pro Arg Leu Ala Ala Glu Thr Gln Pro Val Thr Asp Ala Ser Pro Met
2005 2010 2015

Lys Arg Ser Ile Ser Thr Leu Ala Gln Arg Pro Arg Gly Thr His Leu
2020 2025 2030

Cys Ser Thr Thr Pro Asp Arg Pro Pro Pro Ser Gln Ala Ser Ser His
2035 2040 2045

His His His His Arg Cys His Arg Arg Arg Asp Arg Lys Gln Arg Ser
2050 2055 2060

Leu Glu Lys Gly Pro Ser Leu Ser Ala Asp Met Asp Gly Ala Pro Ser
2065 2070 2075 2080

Ser Ala Val Gly Pro Gly Leu Pro Pro Gly Glu Gly Pro Thr Gly Cys
2085 2090 2095

Arg Arg Glu Arg Glu Arg Arg Gln Glu Arg Ser Arg Ser Gln Glu Arg
2100 2105 2110

Arg Gln Pro Ser Ser Ser Ser Ser Glu Lys Gln Arg Phe Tyr Ser Cys
2115 2120 2125

Asp Arg Phe Gly Gly Arg Glu Pro Pro Lys Pro Lys Pro Ser Leu Ser
2130 2135 2140

Ser His Pro Thr Ser Pro Thr Ala Gly Gln Glu Pro Gly Pro His Pro
2145 2150 2155 2160

Gln Gly Ser Gly Ser Val Asn Gly Ser Pro Leu Leu Ser Thr Ser Gly
2165 2170 2175

Ala Ser Thr Pro Gly Arg Gly Gly Arg Arg Gln Leu Pro Gln Thr Pro
2180 2185 2190

Leu Thr Pro Arg Pro Ser Ile Thr Tyr Lys Thr Ala Asn Ser Ser Pro
2195 2200 2205

Ile His Phe Ala Gly Ala Gln Thr Ser Leu Pro Ala Phe Ser Pro Gly
2210 2215 2220

Arg Leu Ser Arg Gly Leu Ser Glu His Asn Ala Leu Leu Gln Arg Asp
2225 2230 2235 2240

Pro Leu Ser Gln Pro Leu Ala Pro Gly Ser Arg Ile Gly Ser Asp Pro

2245 2250 2255

Tyr Leu Gly Gln Arg Leu Asp Ser Glu Ala Ser Val His Ala Leu Pro
2260 2265 2270

Glu Asp Thr Leu Thr Phe Glu Glu Ala Val Ala Thr Asn Ser Gly Arg
2275 2280 2285

Ser Ser Arg Thr Ser Tyr Val Ser Ser Leu Thr Ser Gln Ser His Pro
2290 2295 2300

Leu Arg Arg Val Pro Asn Gly Tyr His Cys Thr Leu Gly Leu Ser Ser
2305 2310 2315 2320
Gly Gly Arg Ala Arg His Ser Tyr His His Pro Asp Gln Asp His Trp
2325 2330 2335

Cys

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3298 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 20..3292

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

TTGATCTTCG ATCGCGAAG ATG GCT GCT GGC TGC CTG CTG GCC TTG ACT CTG
52
Met Ala Ala Gly Cys Leu Leu Ala Leu Thr Leu
2340 2345

ACA CTT TTC CAA TCT TTG CTC ATC GGC CCC TCG TCG GAG GAG CCG TTC
100
Thr Leu Phe Gln Ser Leu Leu Ile Gly Pro Ser Ser Glu Glu Pro Phe
2350 2355 2360

CCT TCG GCC GTC ACT ATC AAA TCA TGG GTG GAT AAG ATG CAA GAA GAC
148
Pro Ser Ala Val Thr Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp
2365 2370 2375 2380

CTT GTC ACA CTG GCA AAA ACA GCA AGT GGA GTC AAT CAG CTT GTT GAT
196
Leu Val Thr Leu Ala Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp
2385 2390 2395

ATT TAT GAG AAA TAT CAA GAT TTG TAT ACT GTG GAA CCA AAT AAT GCA
244
Ile Tyr Glu Lys Tyr Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala
2400 2405 2410

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CGC CAG CTG GTA GAA ATT GCA GCC AGG GAT ATT GAG AAA CTT CTG AGC
292
Arg Gln Leu Val Glu Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser
      2415                2420                2425

AAC AGA TCT AAA GCC CTG GTG AGC CTG GCA TTG GAA GCG GAG AAA GTT
340
Asn Arg Ser Lys Ala Leu Val Ser Leu Ala Leu Glu Ala Glu Lys Val
    2430                2435                2440

CAA GCA GCT CAC CAG TGG AGA GAA GAT TTT GCA AGC AAT GAA GTT GTC
388
Gln Ala Ala His Gln Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val
2445                2450                2455                2460

TAC TAC AAT GCA AAG GAT GAT CTC GAT CCT GAG AAA AAT GAC AGT GAG
436
Tyr Tyr Asn Ala Lys Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu
                2465                2470                2475

CCA GGC AGC CAG AGG ATA AAA CCT GTT TTC ATT GAA GAT GCT AAT TTT
484
Pro Gly Ser Gln Arg Ile Lys Pro Val Phe Ile Glu Asp Ala Asn Phe
            2480                2485                2490

GGA CGA CAA ATA TCT TAT CAG CAC GCA GCA GTC CAT ATT CCT ACT GAC
532
Gly Arg Gln Ile Ser Tyr Gln His Ala Ala Val His Ile Pro Thr Asp
      2495                2500                2505

ATC TAT GAG GGC TCA ACA ATT GTG TTA AAT GAA CTC AAC TGG ACA AGT
580
Ile Tyr Glu Gly Ser Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser
    2510                2515                2520

GCC TTA GAT GAA GTT TTC AAA AAG AAT CGC GAG GAA GAC CCT TCA TTA
628
Ala Leu Asp Glu Val Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu
2525                2530                2535                2540

TTG TGG CAG GTT TTT GGC AGT GCC ACT GGC CTA GCT CGA TAT TAT CCA
676
Leu Trp Gln Val Phe Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro
                2545                2550                2555

GCT TCA CCA TGG GTT GAT AAT AGT AGA ACT CCA AAT AAG ATT GAC CTT
724
Ala Ser Pro Trp Val Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu
            2560                2565                2570

TAT GAT GTA CGC AGA AGA CCA TGG TAC ATC CAA GGA GCT GCA TCT CCT
772
Tyr Asp Val Arg Arg Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro
      2575                2580                2585

AAA GAC ATG CTT ATT CTG GTG GAT GTG AGT GGA AGT GTT AGT GGA TTG
820
Lys Asp Met Leu Ile Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu
    2590                2595                2600

ACA CTT AAA CTG ATC CGA ACA TCT GTC TCC GAA ATG TTA GAA ACC CTC
868
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Thr Leu Lys Leu Ile Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu
2605 2610 2615 2620

TCA GAT GAT GAT TTC GTG AAT GTA GCT TCA TTT AAC AGC AAT GCT CAG
916
Ser Asp Asp Asp Phe Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln
2625 2630 2635

GAT GTA AGC TGT TTT CAG CAC CTT GTC CAA GCA AAT GTA AGA AAT AAA
964
Asp Val Ser Cys Phe Gln His Leu Val Gln Ala Asn Val Arg Asn Lys
2640 2645 2650

AAA GTG TTG AAA GAC GCG GTG AAT AAT ATC ACA GCC AAA GGA ATT ACA
1012
Lys Val Leu Lys Asp Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr
2655 2660 2665

GAT TAT AAG AAG GGC TTT AGT TTT GCT TTT GAA CAG CTG CTT AAT TAT
1060
Asp Tyr Lys Lys Gly Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr
2670 2675 2680

AAT GTT TCC AGA GCA AAC TGC AAT AAG ATT ATT ATG CTA TTC ACG GAT
1108
Asn Val Ser Arg Ala Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp
2685 2690 2695 2700

GGA GGA GAA GAG AGA GCC CAG GAG ATA TTT AAC AAA TAC AAT AAA GAT
1156
Gly Gly Glu Glu Arg Ala Gln Glu Ile Phe Asn Lys Tyr Asn Lys Asp
2705 2710 2715

AAA AAA GTA CGT GTA TTC AGG TTT TCA GTT GGT CAA CAC AAT TAT GAG
1204
Lys Lys Val Arg Val Phe Arg Phe Ser Val Gly Gln His Asn Tyr Glu
2720 2725 2730

AGA GGA CCT ATT CAG TGG ATG GCC TGT GAA AAC AAA GGT TAT TAT TAT
1252
Arg Gly Pro Ile Gln Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr
2735 2740 2745

GAA ATT CCT TCC ATT GGT GCA ATA AGA ATC AAT ACT CAG GAA TAT TTG
1300
Glu Ile Pro Ser Ile Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu
2750 2755 2760

GAT GTT TTG GGA AGA CCA ATG GTT TTA GCA GGA GAC AAA GCT AAG CAA
1348
Asp Val Leu Gly Arg Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln
2765 2770 2775 2780

GTC CAA TGG ACA AAT GTG TAC CTG GAT GCA TTG GAA CTG GGA CTT GTC
1396
Val Gln Trp Thr Asn Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val
2785 2790 2795

ATT ACT GGA ACT CTT CCG GTC TTC AAC ATA ACC GGC CAA TTT GAA AAT
1444
Ile Thr Gly Thr Leu Pro Val Phe Asn Ile Thr Gly Gln Phe Glu Asn
2800 2805 2810

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AAG ACA AAC TTA AAG AAC CAG CTG ATT CTT GGT GTG ATG GGA GTA GAT
1492
Lys Thr Asn Leu Lys Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp
        2815                2820                2825

GTG TCT TTG GAA GAT ATT AAA AGA CTG ACA CCA CGT TTT ACA CTG TGC
1540
Val Ser Leu Glu Asp Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys
    2830                2835                2840

CCC AAT GGG TAT TAC TTT GCA ATC GAT CCT AAT GGT TAT GCT TTA TTA
1588
Pro Asn Gly Tyr Tyr Phe Ala Ile Asp Pro Asn Gly Tyr Ala Leu Leu
2845                2850                2855                2860

CAT CCA AAT CTT CAG CCA AAG AAC CCC AAA TCT CAG GAG CCA GTA ACA
1636
His Pro Asn Leu Gln Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr
                2865                2870                2875

TTG GAT TTC CTT GAT GCA GAG TTA GAG AAT GAT ATT AAA GTG GAG ATT
1684
Leu Asp Phe Leu Asp Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile
            2880                2885                2890

CGA AAT AAG ATG ATT GAT GGG GAA AGT GGA GAA AAA ACA TTC AGA ACT
1732
Arg Asn Lys Met Ile Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr
        2895                2900                2905

CTG GTT AAA TCT CAA GAT GAG AGA TAT ATT GAC AAA GGA AAC AGG ACA
1780
Leu Val Lys Ser Gln Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr
    2910                2915                2920

TAC ACA TGG ACA CCT GTC AAT GGC ACA GAT TAC AGT TTG GCC TTG GTA
1828
Tyr Thr Trp Thr Pro Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val
2925                2930                2935                2940

TTA CCA ACC TAC AGT TTT TAC TAT ATA AAA GCC AAA CTA GAA GAG ACA
1876
Leu Pro Thr Tyr Ser Phe Tyr Tyr Ile Lys Ala Lys Leu Glu Glu Thr
                2945                2950                2955

ATA ACT CAG GCC AGA TCA AAA AAG GGC AAA ATG AAG GAT TCG GAA ACC
1924
Ile Thr Gln Ala Arg Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr
            2960                2965                2970

CTG AAG CCA GAT AAT TTT GAA GAA TCT GGC TAT ACA TTC ATA GCA CCA
1972
Leu Lys Pro Asp Asn Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro
        2975                2980                2985

AGA GAT TAC TGC AAT GAC CTG AAA ATA TCG GAT AAT AAC ACT GAA TTT
2020
Arg Asp Tyr Cys Asn Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe
    2990                2995                3000
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CTT TTA AAT TTC AAC GAG TTT ATT GAT AGA AAA ACT CCA AAC AAC CCA
2068
Leu Leu Asn Phe Asn Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro
3005                 3010                 3015                 3020

TCA TGT AAC GCG GAT TTG ATT AAT AGA GTC TTG CTT GAT GCA GGC TTT
2116
Ser Cys Asn Ala Asp Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe
                3025                 3030                 3035

ACA AAT GAA CTT GTC CAA AAT TAC TGG AGT AAG CAG AAA AAT ATC AAG
2164
Thr Asn Glu Leu Val Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys
            3040                 3045                 3050

GGA GTG AAA GCA CGA TTT GTT GTG ACT GAT GGT GGG ATT ACC AGA GTT
2212
Gly Val Lys Ala Arg Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val
        3055                 3060                 3065

TAT CCC AAA GAG GCT GGA GAA AAT TGG CAA GAA AAC CCA GAG ACA TAT
2260
Tyr Pro Lys Glu Ala Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr
    3070                 3075                 3080

GAG GAC AGC TTC TAT AAA AGG AGC CTA GAT AAT GAT AAC TAT GTT TTC
2308
Glu Asp Ser Phe Tyr Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe
3085                 3090                 3095                 3100

ACT GCT CCC TAC TTT AAC AAA AGT GGA CCT GGT GCC TAT GAA TCG GGC
2356
Thr Ala Pro Tyr Phe Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly
                3105                 3110                 3115

ATT ATG GTA AGC AAA GCT GTA GAA ATA TAT ATT CAA GGG AAA CTT CTT
2404
Ile Met Val Ser Lys Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu
            3120                 3125                 3130

AAA CCT GCA GTT GTT GGA ATT AAA ATT GAT GTA AAT TCC TGG ATA GAG
2452
Lys Pro Ala Val Val Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu
        3135                 3140                 3145

AAT TTC ACC AAA ACC TCA ATC AGA GAT CCG TGT GCT GGT CCA GTT TGT
2500
Asn Phe Thr Lys Thr Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys
    3150                 3155                 3160

GAC TGC AAA AGA AAC AGT GAC GTA ATG GAT TGT GTG ATT CTG GAT GAT
2548
Asp Cys Lys Arg Asn Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp
3165                 3170                 3175                 3180

GGT GGG TTT CTT CTG ATG GCA AAT CAT GAT GAT TAT ACT AAT CAG ATT
2596
Gly Gly Phe Leu Leu Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile
                3185                 3190                 3195

GGA AGA TTT TTT GGA GAG ATT GAT CCC AGC TTG ATG AGA CAC CTG GTT
2644
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Gly Arg Phe Phe Gly Glu Ile Asp Pro Ser Leu Met Arg His Leu Val
            3200                3205                3210

AAT ATA TCA GTT TAT GCT TTT AAC AAA TCT TAT GAT TAT CAG TCA GTA
2692
Asn Ile Ser Val Tyr Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val
        3215                3220                3225

TGT GAG CCC GGT GCT GCA CCA AAA CAA GGA GCA GGA CAT CGC TCA GCA
2740
Cys Glu Pro Gly Ala Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala
    3230                3235                3240

TAT GTG CCA TCA GTA GCA GAC ATA TTA CAA ATT GGC TGG TGG GCC ACT
2788
Tyr Val Pro Ser Val Ala Asp Ile Leu Gln Ile Gly Trp Trp Ala Thr
3245                3250                3255                3260

GCT GCT GCC TGG TCT ATT CTA CAG CAG TTT CTC TTG AGT TTG ACC TTT
2836
Ala Ala Ala Trp Ser Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe
                3265                3270                3275

CCA CGA CTC CTT GAG GCA GTT GAG ATG GAG GAT GAT GAC TTC ACG GCC
2884
Pro Arg Leu Leu Glu Ala Val Glu Met Glu Asp Asp Phe Thr Ala
            3280                3285                3290

TCC CTG TCC AAG CAG AGC TGC ATT ACT GAA CAA ACC CAG TAT TTC TTC
2932
Ser Leu Ser Lys Gln Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe
        3295                3300                3305

GAT AAC GAC AGT AAA TCA TTC AGT GGT GTA TTA GAC TGT GGA AAC TGT
2980
Asp Asn Asp Ser Lys Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys
    3310                3315                3320

TCC AGA ATC TTT CAT GGA GAA AAG CTT ATG AAC ACC AAC TTA ATA TTC
3028
Ser Arg Ile Phe His Gly Glu Lys Leu Met Asn Thr Asn Leu Ile Phe
3325                3330                3335                3340

ATA ATG GTT GAG AGC AAA GGG ACA TGT CCA TGT GAC ACA CGA CTG CTC
3076
Ile Met Val Glu Ser Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu
                3345                3350                3355

ATA CAA GCG GAG CAG ACT TCT GAC GGT CCA AAT CCT TGT GAC ATG GTT
3124
Ile Gln Ala Glu Gln Thr Ser Asp Gly Pro Asn Pro Cys Asp Met Val
            3360                3365                3370

AAG CAA CCT AGA TAC CGA AAA GGG CCT GAT GTC TGC TTT GAT AAC AAT
3172
Lys Gln Pro Arg Tyr Arg Lys Gly Pro Asp Val Cys Phe Asp Asn Asn
        3375                3380                3385

GTC TTG GAG GAT TAT ACT GAC TGT GGT GGT GTT TCT GGA TTA AAT CCC
3220
Val Leu Glu Asp Tyr Thr Asp Cys Gly Gly Val Ser Gly Leu Asn Pro
    3390                3395                3400
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TCC CTG TGG TAT ATC ATT GGA ATC CAG TTT CTA CTA CTT TGG CTG GTA
3268
Ser Leu Trp Tyr Ile Ile Gly Ile Gln Phe Leu Leu Leu Trp Leu Val
3405 3410 3415 3420

TCT GGC AGC ACA CAC CGG CTG TTA TGACCT
3298
Ser Gly Ser Thr His Arg Leu Leu
3425

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1091 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Ala Ala Gly Cys Leu Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser
1 5 10 15

Leu Leu Ile Gly Pro Ser Ser Glu Glu Pro Phe Pro Ser Ala Val Thr
20 25 30

Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
35 40 45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
50 55 60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
65 70 75 80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
85 90 95

Leu Val Ser Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
100 105 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
115 120 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
130 135 140

Ile Lys Pro Val Phe Ile Glu Asp Ala Asn Phe Gly Arg Gln Ile Ser
145 150 155 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
165 170 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
180 185 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
195 200 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val

210 215 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225 230 235 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
245 250 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
260 265 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
275 280 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
290 295 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305 310 315 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
325 330 335

Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
340 345 350

Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
355 360 365

Ala Gln Glu Ile Phe Asn Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
370 375 380

Phe Arg Phe Ser Val Gly Gln His Asn Tyr Glu Arg Gly Pro Ile Gln
385 390 395 400

Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
405 410 415

Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
420 425 430

Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
435 440 445

Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
450 455 460

Pro Val Phe Asn Ile Thr Gly Gln Phe Glu Asn Lys Thr Asn Leu Lys
465 470 475 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
485 490 495

Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
500 505 510

Phe Ala Ile Asp Pro Asn Gly Tyr Ala Leu Leu His Pro Asn Leu Gln
515 520 525

Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
530 535 540

Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile

545 550 555 560

Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
565 570 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
595 600 605

Phe Tyr Tyr Ile Lys Ala Lys Leu Glu Glu Thr Ile Thr Gln Ala Arg
610 615 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
625 630 635 640

Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
645 650 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
660 665 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Ala Asp
675 680 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
690 695 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
705 710 715 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
725 730 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
740 745 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
755 760 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
770 775 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785 790 795 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
805 810 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
835 840 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
850 855 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865 870 875 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
885 890 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Val
900 905 910

Ala Asp Ile Leu Gln Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
915 920 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
930 935 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945 950 955 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
965 970 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
980 985 990

Gly Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
995 1000 1005

Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln
1010 1015 1020

Thr Ser Asp Gly Pro Asn Pro Cys Asp Met Val Lys Gln Pro Arg Tyr
1025 1030 1035 1040

Arg Lys Gly Pro Asp Val Cys Phe Asp Asn Asn Val Leu Glu Asp Tyr
1045 1050 1055

Thr Asp Cys Gly Gly Val Ser Gly Leu Asn Pro Ser Leu Trp Tyr Ile
1060 1065 1070

Ile Gly Ile Gln Phe Leu Leu Leu Trp Leu Val Ser Gly Ser Thr His
1075 1080 1085

Arg Leu Leu
1090

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1476 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 8..1459

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CTCCCCC ATG TAT GAC GAC TCC TAC GTG CCC GGG TTT GAG GAC TCG GAG
49

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        Met Tyr Asp Asp Ser Tyr Val Pro Gly Phe Glu Asp Ser Glu
                    1095                1100                1105

GCG GGT TCA GCC GAC TCC TAC ACC AGC CGC CCA TCT CTG GAC TCA GAC
97
Ala Gly Ser Ala Asp Ser Tyr Thr Ser Arg Pro Ser Leu Asp Ser Asp
                1110                1115                1120

GTC TCC CTG GAG GAG GAC CGG GAG AGT GCC CGG CGT GAA GTA GAG AGC
145
Val Ser Leu Glu Glu Asp Arg Glu Ser Ala Arg Arg Glu Val Glu Ser
            1125                1130                1135

CAG GCT CAG CAG CAG CTC GAA AGG GCC AAG CAC AAA CCT GTG GCA TTT
193
Gln Ala Gln Gln Gln Leu Glu Arg Ala Lys His Lys Pro Val Ala Phe
        1140                1145                1150

GCG GTG AGG ACC AAT GTC AGC TAC TGT GGC GTA CTG GAT GAG GAG TGC
241
Ala Val Arg Thr Asn Val Ser Tyr Cys Gly Val Leu Asp Glu Glu Cys
    1155                1160                1165

CCA GTC CAG GGC TCT GGA GTC AAC TTT GAG GCC AAA GAT TTT CTG CAC
289
Pro Val Gln Gly Ser Gly Val Asn Phe Glu Ala Lys Asp Phe Leu His
1170                1175                1180                1185

ATT AAA GAG AAG TAC AGC AAT GAC TGG TGG ATC GGG CGG CTA GTG AAA
337
Ile Lys Glu Lys Tyr Ser Asn Asp Trp Trp Ile Gly Arg Leu Val Lys
                1190                1195                1200

GAG GGC GGG GAC ATC GCC TTC ATC CCC AGC CCC CAG CGC CTG GAG AGC
385
Glu Gly Gly Asp Ile Ala Phe Ile Pro Ser Pro Gln Arg Leu Glu Ser
            1205                1210                1215

ATC CGG CTC AAA CAG GAG CAG AAG GCC AGG AGA TCT GGG AAC CCT TCC
433
Ile Arg Leu Lys Gln Glu Gln Lys Ala Arg Arg Ser Gly Asn Pro Ser
        1220                1225                1230

AGC CTG AGT GAC ATT GGC AAC CGA CGC TCC CCT CCG CCA TCT CTA GCC
481
Ser Leu Ser Asp Ile Gly Asn Arg Arg Ser Pro Pro Pro Ser Leu Ala
    1235                1240                1245

AAG CAG AAG CAA AAG CAG GCG GAA CAT GTT CCC CCA TAT GAC GTG GTG
529
Lys Gln Lys Gln Lys Gln Ala Glu His Val Pro Pro Tyr Asp Val Val
1250                1255                1260                1265

CCC TCC ATG CGG CCT GTG GTG CTG GTG GGA CCC TCT CTG AAA GGT TAT
577
Pro Ser Met Arg Pro Val Val Leu Val Gly Pro Ser Leu Lys Gly Tyr
                1270                1275                1280

GAG GTC ACA GAC ATG ATG CAG AAG GCT CTC TTC GAC TTC CTC AAA CAC
625
Glu Val Thr Asp Met Met Gln Lys Ala Leu Phe Asp Phe Leu Lys His
            1285                1290                1295
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AGA TTT GAT GGC AGG ATC TCC ATC ACC CGA GTC ACA GCC GAC CTC TCC
673
Arg Phe Asp Gly Arg Ile Ser Ile Thr Arg Val Thr Ala Asp Leu Ser
        1300                1305                1310

CTG GCA AAG CGA TCT GTG CTC AAC AAT CCG GGC AAG AGG ACC ATC ATT
721
Leu Ala Lys Arg Ser Val Leu Asn Asn Pro Gly Lys Arg Thr Ile Ile
    1315                1320                1325

GAG CGC TCC TCT GCC CGC TCC AGC ATT GCG GAA GTG CAG AGT GAG ATC
769
Glu Arg Ser Ser Ala Arg Ser Ser Ile Ala Glu Val Gln Ser Glu Ile
1330                1335                1340                1345

GAG CGC ATA TTT GAG CTG GCC AAA TCC CTG CAG CTA GTA GTG TTG GAC
817
Glu Arg Ile Phe Glu Leu Ala Lys Ser Leu Gln Leu Val Val Leu Asp
                1350                1355                1360
GCT GAC ACC ATC AAC CAC CCA GCA CAG CTG GCC AAG ACC TCG CTG GCC
865
Ala Asp Thr Ile Asn His Pro Ala Gln Leu Ala Lys Thr Ser Leu Ala
            1365                1370                1375

CCC ATC ATC GTC TTT GTC AAA GTG TCC TCA CCA AAG GTA CTC CAG CGT
913
Pro Ile Ile Val Phe Val Lys Val Ser Ser Pro Lys Val Leu Gln Arg
        1380                1385                1390

CTC ATT CGC TCC CGG GGG AAG TCA CAG ATG AAG CAC CTG ACC GTA CAG
961
Leu Ile Arg Ser Arg Gly Lys Ser Gln Met Lys His Leu Thr Val Gln
    1395                1400                1405

ATG ATG GCA TAT GAT AAG CTG GTT CAG TGC CCA CCG GAG TCA TTT GAT
1009
Met Met Ala Tyr Asp Lys Leu Val Gln Cys Pro Pro Glu Ser Phe Asp
1410                1415                1420                1425

GTG ATT CTG GAT GAG AAC CAG CTG GAG GAT GCC TGT GAG CAC CTG GCT
1057
Val Ile Leu Asp Glu Asn Gln Leu Glu Asp Ala Cys Glu His Leu Ala
                1430                1435                1440

GAG TAC CTG GAG GTT TAC TGG CGG GCC ACG CAC CAC CCA GCC CCT GGC
1105
Glu Tyr Leu Glu Val Tyr Trp Arg Ala Thr His His Pro Ala Pro Gly
            1445                1450                1455

CCC GGA CTT CTG GGT CCT CCC AGT GCC ATC CCC GGA CTT CAG AAC CAG
1153
Pro Gly Leu Leu Gly Pro Pro Ser Ala Ile Pro Gly Leu Gln Asn Gln
        1460                1465                1470

CAG CTG CTG GGG GAG CGT GGC GAG GAG CAC TCC CCC CTT GAG CGG GAC
1201
Gln Leu Leu Gly Glu Arg Gly Glu Glu His Ser Pro Leu Glu Arg Asp
    1475                1480                1485

AGC TTG ATG CCC TCT GAT GAG GCC AGC GAG AGC TCC CGC CAA GCC TGG
1249
```

Ser Leu Met Pro Ser Asp Glu Ala Ser Glu Ser Ser Arg Gln Ala Trp
1490 1495 1500 1505

ACA GGA TCT TCA CAG CGT AGC TCC CGC CAC CTG GAG GAG GAC TAT GCA
1297
Thr Gly Ser Ser Gln Arg Ser Ser Arg His Leu Glu Glu Asp Tyr Ala
1510 1515 1520

GAT GCC TAC CAG GAC CTG TAC CAG CCT CAC CGC CAA CAC ACC TCG GGG
1345
Asp Ala Tyr Gln Asp Leu Tyr Gln Pro His Arg Gln His Thr Ser Gly
1525 1530 1535

CTG CCT AGT GCT AAC GGG CAT GAC CCC CAA GAC CGG CTT CTA GCC CAG
1393
Leu Pro Ser Ala Asn Gly His Asp Pro Gln Asp Arg Leu Leu Ala Gln
1540 1545 1550

GAC TCA GAA CAC AAC CAC AGT GAC CGG AAC TGG CAG CGC AAC CGG CCT
1441
Asp Ser Glu His Asn His Ser Asp Arg Asn Trp Gln Arg Asn Arg Pro
1555 1560 1565

TGG CCC AAG GAT AGC TAC TGACAGCCTC CTGCTGC
1476
Trp Pro Lys Asp Ser Tyr
1570 1575

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 484 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Met Tyr Asp Asp Ser Tyr Val Pro Gly Phe Glu Asp Ser Glu Ala Gly
1 5 10 15

Ser Ala Asp Ser Tyr Thr Ser Arg Pro Ser Leu Asp Ser Asp Val Ser
20 25 30

Leu Glu Glu Asp Arg Glu Ser Ala Arg Arg Glu Val Glu Ser Gln Ala
35 40 45

Gln Gln Gln Leu Glu Arg Ala Lys His Lys Pro Val Ala Phe Ala Val
50 55 60

Arg Thr Asn Val Ser Tyr Cys Gly Val Leu Asp Glu Glu Cys Pro Val
65 70 75 80

Gln Gly Ser Gly Val Asn Phe Glu Ala Lys Asp Phe Leu His Ile Lys
85 90 95

Glu Lys Tyr Ser Asn Asp Trp Trp Ile Gly Arg Leu Val Lys Glu Gly
100 105 110

Gly Asp Ile Ala Phe Ile Pro Ser Pro Gln Arg Leu Glu Ser Ile Arg

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Ser Ala Asn Gly His Asp Pro Gln Asp Arg Leu Leu Ala Gln Asp Ser
    450                 455                 460

Glu His Asn His Ser Asp Arg Asn Trp Gln Arg Asn Arg Pro Trp Pro
465                 470                 475                 480

Lys Asp Ser Tyr
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What is claimed is:

1. An isolated nucleic acid encoding a calcium channel a1B subunit, wherein the nucleic acid has the nucleotide A at position 194, or the nucleotide G at position 2559.

2. The isolated nucleic acid of Claim 1, wherein the nucleic acid has the nucleotide A at position 6470.

3. The isolated nucleic acid of Claim 1, wherein the nucleic acid has a deletion of nucleotides 4814-4819.

4. The isolated nucleic acid of Claim 1, wherein the nucleic acid is isolatable from human cerebellum tissue.

5. A vector comprising the isolated nucleic acid of Claim 1.

6. A host cell comprising the vector of Claim 5.

7. An isolated nucleic acid encoding a calcium channel b3 subunit, wherein the nucleic acid has at least one of the following: a G at position 46; a T at position 203; a T at position 300; a G at position 303; a G at position 420; a T at position 438; a C at position 477; a G at position 486; an A at position 534; a C at position 552; a T at position 561; an A at position 1064; a GC as positions 1283-4; and a T at position 1308.

8. An isolated nucleic acid encoding a calcium channel b3 subunit, wherein the nucleic acid has the nucleotides TCC inserted at position 119, or the nucleotides ATG insert d at position 978.

9. A v ctor comprising the isolated nucleic acid of Claim 7.

10. A host cell comprising the vector of Claim 9.

11. The isolated nucleic acid of Claim 7, wherein the nucleic acid is isolatable from human cerebellum tissue.

12. A protein encoded the nucleic acid of Claim 1.

13. An antibody to the protein of Claim 12.

14. A fusion protein comprising a protein encoded by the nucleic acid of Claim 1.

15. A protein encoded the nucleic acid of Claim 7.

16. An antibody to the protein of Claim 15.

17. A fusion protein comprising a protein encoded by the nucleic acid of Claim 7.

18. An isolated human calcium channel, comprising subunits encoded by the nucleic acids having the sequences of SEQ ID NO. 1, SEQ ID NO. 3, and SEQ ID NO. 5.

19. A method of identifying an agent which modulates the activity of a calcium channel, comprising the steps of:

a. maintaining a host cell that expresses a functional calcium channel in a solution containing the agent to be tested and a calcium channel-selectiv ion, wherein the functional calcium channel comprises an a1B subunit having the nucleotide A at position 194, or the nucleotide G at position 2559; or a b3 subunit having a G at position 46; a T at position 203; a T at position 300; a G at position 303; a G at position 420; a T at position 438; a C at position 477; a G at position 486; an A at position 534; a C at position 552; a T at position 561; an A at position

1064; a GC as positions 1283-4; or a T at position 1308;

b. depolarizing the cell membrane of the host cell; and

c. detecting the current flowing into the cell, wherein if the current that is detected differs from that produced by a control cell maintained in a solution containing the calcium channel-selective ion, but not the agent to be tested, then the agent is an agent which modulated calcium channel activity.

20. An agent identified by the method of Claim 19.

Segment from ACHALPHA1B (1 to 7266) to be translated: 92:7105

Segment from ACHALPHA1B (1 to 7266) to be translated:

```
          10         20         30         40         50         60
TCCGTGGCTG CTCCGCTCTG AGCGCCTGGC GCGCCCCGCG CCCTCCCTGC CGGGGCCGCT GGGCCGGG

          80         90        100        109        118        127
TGCACGCGGG GCCCGGGAGC C ATG GTC CGC TTC GGG GAC GAG CTG GGC GGC CGC TAT
                        MET Val Arg Phe Gly Asp Glu Leu Gly Gly Arg Tyr

         136        145        154        163        172        181
GGA GGC CCC GGC AGC GGA GAG CGG GCC CGG GGC GGC GGG GCC GGC GGG GCG GGG
Gly Gly Pro Gly Ser Gly Glu Arg Ala Arg Gly Gly Gly Ala Gly Gly Ala Gly

         190        199        208        217        226        235
GGC CCG GGT CCC GGG GGG CTG CAG CCC GGC CAG CGG GTC CTC TAC AAG CAA TCG
Gly Pro Gly Pro Gly Gly Leu Gln Pro Gly Gln Arg Val Leu Tyr Lys Gln Ser

         244        253        262        271        280        289
ATC GCG CAG CGC GCG CGG ACC ATG GCG CTG TAC AAC CCC ATC CCG GTC AAG CAG
Ile Ala Gln Arg Ala Arg Thr MET Ala Leu Tyr Asn Pro Ile Pro Val Lys Gln

         298        307        316        325        334        343
AAC TGC TTC ACC GTC AAC CGC TCG CTC TTC GTC TTC AGC GAG GAC AAC GTC GTC
Asn Cys Phe Thr Val Asn Arg Ser Leu Phe Val Phe Ser Glu Asp Asn Val Val

         352        361        370        379        388        397
CGC AAA TAC GCG AAG CGC ATC ACC GAG TGG CCT CCA TTC GAG TAT ATG ATC CTG
Arg Lys Tyr Ala Lys Arg Ile Thr Glu Trp Pro Pro Phe Glu Tyr MET Ile Leu

         406        415        424        433        442        451
GCC ACC ATC ATC GCC AAC TGC ATC GTG CTG GCC CTG GAG CAG CAC CTC CCT GAT
Ala Thr Ile Ile Ala Asn Cys Ile Val Leu Ala L u Glu Gln His Leu Pro Asp

         460        469        478        487        496        505
GGG GAC AAA ACG CCC ATG TCC GAG CGG CTG GAC GAC ACG GAG CCC TAT TTC ATC
```

FIG. 1

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Gly Asp Lys Thr Pro MET Ser Glu Arg Leu Asp Asp Thr Glu Pro Tyr Phe Ile
        514         523         532         541         550         559
GGG ATC TTT TGC TTC GAG GCA GGG ATC AAA ATC ATC GCT CTG GGC TTT GTC TTC
Gly Ile Phe Cys Phe Glu Ala Gly Ile Lys Ile Ile Ala Leu Gly Phe Val Phe
        568         577         586         595         604         613
CAC AAG GGC TCT TAC CTG CGG AAC GGC TGG AAC GTC ATG GAC TTC GTG GTC GTC
His Lys Gly Ser Tyr Leu Arg Asn Gly Trp Asn Val MET Asp Phe Val Val Val
        622         631         640         649         658         667
CTC ACA GGG ATC CTT GCC ACG GCT GGA ACT GAC TTC GAC CTG CGA ACA CTG AGG
Leu Thr Gly Ile Leu Ala Thr Ala Gly Thr Asp Phe Asp Leu Arg Thr Leu Arg
        676         685         694         703         712         721
GCT GTG CGT GTG CTG AGG CCC CTG AAG CTG GTG TCT GGG ATT CCA AGT TTG CAG
Ala Val Arg Val Leu Arg Pro Leu Lys Leu Val Ser Gly Ile Pro Ser Leu Gln
        730         739         748         757         766         775
GTG GTG CTC AAG TCC ATC ATG AAG GCC ATG GTT CCA CTC CTG CAG ATT GGG CTG
Val Val Leu Lys Ser Ile MET Lys Ala MET Val Pro Leu Leu Gln Ile Gly Leu
        784         793         802         811         820         829
CTT CTC TTC TTT GCC ATC CTC ATG TTT GCC ATC ATT GGC CTG GAG TTC TAC ATG
Leu Leu Phe Phe Ala Ile Leu MET Phe Ala Ile Ile Gly Leu Glu Phe Tyr MET
        838         847         856         865         874         883
GGC AAG TTC CAC AAG GCC TGT TTC CCC AAC AGC ACA GAT GCG GAG CCC GTG GGT
Gly Lys Phe His Lys Ala Cys Phe Pro Asn Ser Thr Asp Ala Glu Pro Val Gly
        892         901         910         919         928         937
GAC TTC CCC TGT GGC AAG GAG GCC CCA GCC CGG CTG TGC GAG GGC GAC ACT GAG
Asp Phe Pro Cys Gly Lys Glu Ala Pro Ala Arg Leu Cys Glu Gly Asp Thr Glu
        946         955         964         973         982         991
TGC CGG GAG TAC TGG CCA GGA CCC AAC TTT GGC ATC ACC AAC TTT GAC AAT ATC
Cys Arg Glu Tyr Trp Pro Gly Pro Asn Phe Gly Ile Thr Asn Phe Asp Asn Ile
       1000        1009        1018        1027        1036        1045
CTG TTT GCC ATC TTG ACG GTG TTC CAG TGC ATC ACC ATG GAG GGC TGG ACT GAC
Leu Phe Ala Ile Leu Thr Val Phe Gln Cys Ile Thr MET Glu Gly Trp Thr Asp
       1054        1063        1072        1081        1090        1099
ATC CTC TAT AAT ACA AAC GAT GCG GCC GGC AAC ACC TGG AAC TGG CTC TAC TTC
Ile Leu Tyr Asn Thr Asn Asp Ala Ala Gly Asn Thr Trp Asn Trp Leu Tyr Phe
       1108        1117        1126        1135        1144        1153
ATC CCT CTC ATC ATC ATC GGC TCC TTC TTC ATG CTC AAC CTG GTG CTG GGC GTG
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Ile Pro Leu Ile Ile Il Gly Ser Phe Phe MET Leu Asn Leu Val Leu Gly Val

1162 1171 1180 1189 1198 1207

CTC TCG GGG GAG TTT GCC AAG GAG CGA GAG AGG GTG GAG AAC CGC CGC GCC TTC
Leu Ser Gly Glu Phe Ala Lys Glu Arg Glu Arg Val Glu Asn Arg Arg Ala Phe

1216 1225 1234 1243 1252 1261

CTG AAG CTG CGC CGG CAG CAG CAG ATC GAG CGA GAG CTC AAC GGG TAC CTG GAG
Leu Lys Leu Arg Arg Gln Gln Gln Ile Glu Arg Glu Leu Asn Gly Tyr Leu Glu

1270 1279 1288 1297 1306 1315

TGG ATC TTC AAG GCG GAG GAA GTC ATG CTG GCC GAG GAG GAC AGG AAT GCA GAG
Trp Ile Phe Lys Ala Glu Glu Val MET Leu Ala Glu Glu Asp Arg Asn Ala Glu

1324 1333 1342 1351 1360 1369

GAG AAG TCC CCT TTG GAC GTG CTG AAG AGA GCG GCC ACC AAG AAG AGC AGA AAT
Glu Lys Ser Pro Leu Asp Val Leu Lys Arg Ala Ala Thr Lys Lys Ser Arg Asn

1378 1387 1396 1405 1414 1423

GAC CTG ATC CAC GCA GAG GAG GGA GAG GAC CGG TTT GCA GAT CTC TGT GCT GTT
Asp Leu Ile His Ala Glu Glu Gly Glu Asp Arg Phe Ala Asp Leu Cys Ala Val

1432 1441 1450 1459 1468 1477

GGA TCC CCC TTC GCC CGC GCC AGC CTC AAG AGC GGG AAG ACA GAG AGC TCG TCA
Gly Ser Pro Phe Ala Arg Ala Ser Leu Lys Ser Gly Lys Thr Glu Ser Ser Ser

1486 1495 1504 1513 1522 1531

TAC TTC CGG AGG AAG GAG AAG ATG TTC CGG TTT TTT ATC CGG CGC ATG GTG AAG
Tyr Phe Arg Arg Lys Glu Lys MET Phe Arg Phe Phe Ile Arg Arg MET Val Lys

1540 1549 1558 1567 1576 1585

GCT CAG AGC TTC TAC TGG GTG GTG CTG TGC GTG GTG GCC CTG AAC ACA CTG TGT
Ala Gln Ser Phe Tyr Trp Val Val Leu Cys Val Val Ala Leu Asn Thr Leu Cys

1594 1603 1612 1621 1630 1639

GTG GCC ATG GTG CAT TAC AAC CAG CCG CGG CGG CTT ACC ACG ACC CTG TAT TTT
Val Ala MET Val His Tyr Asn Gln Pro Arg Arg Leu Thr Thr Thr Leu Tyr Phe

1648 1657 1666 1675 1684 1693

GCA GAG TTT GTT TTC CTG GGT CTC TTC CTC ACA GAG ATG TCC CTG AAG ATG TAT
Ala Glu Phe Val Phe Leu Gly Leu Phe Leu Thr Glu MET Ser Leu Lys MET Tyr

1702 1711 1720 1729 1738 1747

GGC CTG GGG CCC AGA AGC TAC TTC CGG TCC TCC TTC AAC TGC TTC GAC TTT GGG
Gly Leu Gly Pro Arg Ser Tyr Phe Arg Ser Ser Phe Asn Cys Phe Asp Phe Gly

1756 1765 1774 1783 1792 1801

GTC ATC GTG GGG AGC GTC TTT GAA GTG GTC TGG GCG GCC ATC AAG CCG GGA AGC

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Val Ile Val Gly Ser Val Phe Glu Val Val Trp Ala Ala Ile Lys Pro Gly S r

      1810        1819        1828        1837        1846        1855

TCC TTT GGG ATC AGT GTG CTG CGG GCC CTC CGC CTG CTG AGG ATC TTC AAA GTC
Ser Phe Gly Ile Ser Val Leu Arg Ala Leu Arg Leu Leu Arg Ile Phe Lys Val

      1864        1873        1882        1891        1900        1909

ACG AAG TAC TGG AGC TCC CTG CGG AAC CTG GTG GTG TCC CTG CTG AAC TCC ATG
Thr Lys Tyr Trp Ser Ser Leu Arg Asn Leu Val Val Ser Leu Leu Asn Ser MET

      1918        1927        1936        1945        1954        1963

AAG TCC ATC ATC AGC CTG CTC TTC TTG CTC TTC CTG TTC ATT GTG GTC TTC GCC
Lys Ser Ile Ile Ser Leu Leu Phe Leu Leu Phe Leu Phe Ile Val Val Phe Ala

      1972        1981        1990        1999        2008        2017

CTG CTG GGG ATG CAG CTG TTT GGG GGA CAG TTC AAC TTC CAG GAT GAG ACT CCC
Leu Leu Gly MET Gln Leu Phe Gly Gly Gln Phe Asn Phe Gln Asp Glu Thr Pro

      2026        2035        2044        2053        2062        2071

ACA ACC AAC TTC GAC ACC TTC CCT GCC GCC ATC CTC ACT GTC TTC CAG ATC CTG
Thr Thr Asn Phe Asp Thr Phe Pro Ala Ala Ile Leu Thr Val Phe Gln Ile Leu

      2080        2089        2098        2107        2116        2125

ACG GGA GAG GAC TGG AAT GCA GTG ATG TAT CAC GGG ATC GAA TCG CAA GGC GGC
Thr Gly Glu Asp Trp Asn Ala Val MET Tyr His Gly Ile Glu Ser Gln Gly Gly

      2134        2143        2152        2161        2170        2179

GTC AGC AAA GGC ATG TTC TCG TCC TTT TAC TTC ATT GTC CTG ACA CTG TTC GGA
Val Ser Lys Gly MET Phe Ser Ser Phe Tyr Phe Ile Val Leu Thr Leu Phe Gly

      2188        2197        2206        2215        2224        2233

AAC TAC ACT CTG CTG AAT GTC TTT CTG GCC ATC GCT GTG GAC AAC CTG GCC AAC
Asn Tyr Thr Leu Leu Asn Val Phe Leu Ala Ile Ala Val Asp Asn Leu Ala Asn

      2242        2251        2260        2269        2278        2287

GCC CAA GAG CTG ACC AAG GAT GAA GAG GAG ATG GAA GAA GCA GCC AAT CAG AAG
Ala Gln Glu Leu Thr Lys Asp Glu Glu Glu MET Glu Glu Ala Ala Asn Gln Lys

      2296        2305        2314        2323        2332        2341

CTT GCT CTG CAA AAG GCC AAA GAA GTG GCT GAA GTC AGC CCC ATG TCT GCC GCG
Leu Ala Leu Gln Lys Ala Lys Glu Val Ala Glu Val Ser Pro MET Ser Ala Ala

      2350        2359        2368        2377        2386        2395

AAC ATC TCC ATC GCC GCC AGG CAG CAG AAC TCG GCC AAG GCG CGC TCG GTG TGG
Asn Ile Ser Ile Ala Ala Arg Gln Gln Asn Ser Ala Lys Ala Arg Ser Val Trp

      2404        2413        2422        2431        2440        2449

GAG CAG CGG GCC AGC CAG CTA CGG CTG CAG AAC CTG CGG GCC AGC TGC GAG GCG
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Glu Gln Arg Ala Ser Gln Leu Arg Leu Gln Asn Leu Arg Ala Ser Cys Glu Ala

2458 2467 2476 2485 2494 2503

CTG TAC AGC GAG ATG GAC CCC GAG GAG CGG CTG CGC TTC GCC ACT ACG CGC CAC
Leu Tyr Ser Glu MET Asp Pro Glu Glu Arg Leu Arg Phe Ala Thr Thr Arg His

2512 2521 2530 2539 2548 2557

CGG CGG CCC GAC ATG AAG ACG CAC CTG GAC CGG CCG CTG GTG GTG GAG CTG GGC
Arg Arg Pro Asp MET Lys Thr His Leu Asp Arg Pro Leu Val Val Glu Leu Gly

2566 2575 2584 2593 2602 2611

CGC GAC GGC GCG CGG GGG CCC GTG GGA GGC AAA GCC CGA CCT GAG GCT GCG GAG
Arg Asp Gly Ala Arg Gly Pro Val Gly Gly Lys Ala Arg Pro Glu Ala Ala Glu

2620 2629 2638 2647 2656 2665

GCC CCC GAG GGC GTC GAC CCT CCG CGC AGG CAC CAC CGG CAC CGC GAC AAG GAC
Ala Pro Glu Gly Val Asp Pro Pro Arg Arg His His Arg His Arg Asp Lys Asp

2674 2683 2692 2701 2710 2719

AAG ACC CCC GCG GCG GGG GAC CAG GAC CGA GCA GAG GCC CCG AAG GCG GAG AGC
Lys Thr Pro Ala Ala Gly Asp Gln Asp Arg Ala Glu Ala Pro Lys Ala Glu Ser

2728 2737 2746 2755 2764 2773

GGG GAG CCC GGT GCC CGG GAG GAG CGG CCG CGG CCG CAC CGC AGC CAC AGC AAG
Gly Glu Pro Gly Ala Arg Glu Glu Arg Pro Arg Pro His Arg Ser His Ser Lys

2782 2791 2800 2809 2818 2827

GAG GCC GCG GGG CCC CCG GAG GCG CGG AGC GAG CGC GGC CGA GGC CCA GGC CCC
Glu Ala Ala Gly Pro Pro Glu Ala Arg Ser Glu Arg Gly Arg Gly Pro Gly Pro

2836 2845 2854 2863 2872 2881

GAG GGC GGC CGG CGG CAC CAC CGG CGC GGC TCC CCG GAG GAG GCG GCC GAG CGG
Glu Gly Gly Arg Arg His His Arg Arg Gly Ser Pro Glu Glu Ala Ala Glu Arg

2890 2899 2908 2917 2926 2935

GAG CCC CGA CGC CAC CGC GCG CAC CGG CAC CAG GAT CCG AGC AAG GAG TGC GCC
Glu Pro Arg Arg His Arg Ala His Arg His Gln Asp Pro Ser Lys Glu Cys Ala

2944 2953 2962 2971 2980 2989

GGC GCC AAG GGC GAG CGG CGC GCG CGG CAC CGC GGC GGC CCC CGA GCG GGG CCC
Gly Ala Lys Gly Glu Arg Arg Ala Arg His Arg Gly Gly Pro Arg Ala Gly Pro

2998 3007 3016 3025 3034 3043

CGG GAG GCG GAG AGC GGG GAG GAG CCG GCG CGG CGG CAC CGG GCC CGG CAC AAG
Arg Glu Ala Glu Ser Gly Glu Glu Pro Ala Arg Arg His Arg Ala Arg His Lys

3052 3061 3070 3079 3088 3097

GCG CAG CCT GCT CAC GAG GCT GTG GAG AAG GAG ACC ACG GAG AAG GAG GCC ACG

```
Ala Gln Pro Ala His Glu Ala Val Glu Lys Glu Thr Thr Glu Lys Glu Ala Thr

      3106        3115        3124        3133        3142        3151

GAG AAG GAG GCT GAG ATA GTG GAA GCC GAC AAG GAA AAG GAG CTC CGG AAC CAC
Glu Lys Glu Ala Glu Ile Val Glu Ala Asp Lys Glu Lys Glu Leu Arg Asn His

      3160        3169        3178        3187        3196        3205

CAG CCC CGG GAG CCA CAC TGT GAC CTG GAG ACC AGT GGG ACT GTG ACT GTG GGT
Gln Pro Arg Glu Pro His Cys Asp Leu Glu Thr Ser Gly Thr Val Thr Val Gly

      3214        3223        3232        3241        3250        3259

CCC ATG CAC ACA CTG CCC AGC ACC TGT CTC CAG AAG GTG GAG GAA CAG CCA GAG
Pro MET His Thr Leu Pro Ser Thr Cys Leu Gln Lys Val Glu Glu Gln Pro Glu

      3268        3277        3286        3295        3304        3313

GAT GCA GAC AAT CAG CGG AAC GTC ACT CGC ATG GGC AGT CAG CCC CCA GAC CCG
Asp Ala Asp Asn Gln Arg Asn Val Thr Arg MET Gly Ser Gln Pro Pro Asp Pro

      3322        3331        3340        3349        3358        3367

AAC ACT ATT GTA CAT ATC CCA GTG ATG CTG ACG GGC CCT CTT GGG GAA GCC ACG
Asn Thr Ile Val His Ile Pro Val MET Leu Thr Gly Pro Leu Gly Glu Ala Thr

      3376        3385        3394        3403        3412        3421

GTC GTT CCC AGT GGT AAC GTG GAC CTG GAA AGC CAA GCA GAG GGG AAG AAG GAG
Val Val Pro Ser Gly Asn Val Asp Leu Glu Ser Gln Ala Glu Gly Lys Lys Glu

      3430        3439        3448        3457        3466        3475

GTG GAA GCG GAT GAC GTG ATG AGG AGC GGC CCC CGG CCT ATC GTC CCA TAC AGC
Val Glu Ala Asp Asp Val MET Arg Ser Gly Pro Arg Pro Ile Val Pro Tyr Ser

      3484        3493        3502        3511        3520        3529

TCC ATG TTC TGT TTA AGC CCC ACC AAC CTG CTC CGC CGC TTC TGC CAC TAC ATC
Ser MET Phe Cys Leu Ser Pro Thr Asn Leu Leu Arg Arg Phe Cys His Tyr Ile

      3538        3547        3556        3565        3574        3583

GTG ACC ATG AGG TAC TTC GAG GTG GTC ATT CTC GTG GTC ATC GCC TTG AGC AGC
Val Thr MET Arg Tyr Phe Glu Val Val Ile Leu Val Val Ile Ala Leu Ser Ser

      3592        3601        3610        3619        3628        3637

ATC GCC CTG GCT GCT GAG GAC CCA GTG CGC ACA GAC TCG CCC AGG AAC AAC GCT
Ile Ala Leu Ala Ala Glu Asp Pro Val Arg Thr Asp Ser Pro Arg Asn Asn Ala

      3646        3655        3664        3673        3682        3691

CTG AAA TAC CTG GAT TAC ATT TTC ACT GGT GTC TTT ACC TTT GAG ATG GTG ATA
Leu Lys Tyr Leu Asp Tyr Ile Phe Thr Gly Val Phe Thr Phe Glu MET Val Ile

      3700        3709        3718        3727        3736        3745

AAG ATG ATC GAC TTG GGA CTG CTG CTT CAC CCT GGA GCC TAT TTC CGG GAC TTG
```

Lys MET Ile Asp Leu Gly Leu Leu Leu His Pro Gly Ala Tyr Phe Arg Asp Leu

3754 3763 3772 3781 3790 3799

TGG AAC ATT CTG GAC TTC ATT GTG GTC AGT GGC GCC CTG GTG GCG TTT GCT TTC
Trp Asn Ile Leu Asp Phe Ile Val Val Ser Gly Ala Leu Val Ala Phe Ala Phe

3808 3817 3826 3835 3844 3853

TCA GGA TCC AAA GGG AAA GAC ATC AAT ACC ATC AAG TCT CTG AGA GTC CTT CGT
Ser Gly Ser Lys Gly Lys Asp Ile Asn Thr Ile Lys Ser Leu Arg Val Leu Arg

3862 3871 3880 3889 3898 3907

GTC CTG CGG CCC CTC AAG ACC ATC AAA CGG CTG CCC AAG CTC AAG GCT GTG TTT
Val Leu Arg Pro Leu Lys Thr Ile Lys Arg Leu Pro Lys Leu Lys Ala Val Phe

3916 3925 3934 3943 3952 3961

GAC TGT GTG GTG AAC TCC CTG AAG AAT GTC CTC AAC ATC TTG ATT GTC TAC ATG
Asp Cys Val Val Asn Ser Leu Lys Asn Val Leu Asn Ile Leu Ile Val Tyr MET

3970 3979 3988 3997 4006 4015

CTC TTC ATG TTC ATA TTT GCC GTC ATT GCG GTG CAG CTC TTC AAA GGG AAG TTT
Leu Phe MET Phe Ile Phe Ala Val Ile Ala Val Gln Leu Phe Lys Gly Lys Ph

4024 4033 4042 4051 4060 4069

TTC TAC TGC ACA GAT GAA TCC AAG GAG CTG GAG AGG GAC TGC AGG GGT CAG TAT
Phe Tyr Cys Thr Asp Glu Ser Lys Glu Leu Glu Arg Asp Cys Arg Gly Gln Tyr

4078 4087 4096 4105 4114 4123

TTG GAT TAT GAG AAG GAG GAA GTG GAA GCT CAG CCC AGG CAG TGG AAG AAA TAC
Leu Asp Tyr Glu Lys Glu Glu Val Glu Ala Gln Pro Arg Gln Trp Lys Lys Tyr

4132 4141 4150 4159 4168 4177

GAC TTT CAC TAC GAC AAT GTG CTC TGG GCT CTG CTG ACG CTG TTC ACA GTG TCC
Asp Phe His Tyr Asp Asn Val Leu Trp Ala Leu Leu Thr Leu Phe Thr Val Ser

4186 4195 4204 4213 4222 4231

ACG GGA GAA GGC TGG CCC ATG GTG CTG AAA CAC TCC GTG GAT GCC ACC TAT GAG
Thr Gly Glu Gly Trp Pro MET Val Leu Lys His Ser Val Asp Ala Thr Tyr Glu

4240 4249 4258 4267 4276 4285

GAG CAG GGT CCA AGC CCT GGG TAC CGC ATG GAG CTG TCC ATC TTC TAC GTG GTC
Glu Gln Gly Pro Ser Pro Gly Tyr Arg MET Glu Leu Ser Ile Phe Tyr Val Val

4294 4303 4312 4321 4330 4339

TAC TTT GTG GTC TTT CCC TTC TTC TTC GTC AAC ATC TTT GTG GCT TTG ATC ATC
Tyr Phe Val Val Phe Pro Phe Phe Phe Val Asn Ile Phe Val Ala Leu Ile Ile

4348 4357 4366 4375 4384 4393

ATC ACC TTC CAG GAG CAG GGG GAC AAG GTG ATG TCT GAA TGC AGC CTG GAG AAG

Ile Thr Phe Gln Glu Gln Gly Asp Lys Val MET Ser Glu Cys Ser Leu Glu Lys

4402 4411 4420 4429 4438 4447

AAC GAG AGG GCT TGC ATT GAC TTC GCC ATC AGC GCC AAA CCC CTG ACA CGG TAC
Asn Glu Arg Ala Cys Ile Asp Phe Ala Ile Ser Ala Lys Pro Leu Thr Arg Tyr

4456 4465 4474 4483 4492 4501

ATG CCC CAA AAC CGG CAG TCG TTC CAG TAT AAG ACG TGG ACA TTT GTG GTC TCC
MET Pro Gln Asn Arg Gln Ser Phe Gln Tyr Lys Thr Trp Thr Phe Val Val Ser

4510 4519 4528 4537 4546 4555

CCG CCC TTT GAA TAC TTC ATC ATG GCC ATG ATA GCC CTC AAC ACT GTG GTG CTG
Pro Pro Phe Glu Tyr Phe Ile MET Ala MET Ile Ala Leu Asn Thr Val Val Leu

4564 4573 4582 4591 4600 4609

ATG ATG AAG TTC TAT GAT GCA CCC TAT GAG TAC GAG CTG ATG CTG AAA TGC CTG
MET MET Lys Phe Tyr Asp Ala Pro Tyr Glu Tyr Glu Leu MET Leu Lys Cys Leu

4618 4627 4636 4645 4654 4663

AAC ATC GTG TTC ACA TCC ATG TTC TCC ATG GAA TGC GTG CTG AAG ATC ATC GCC
Asn Ile Val Phe Thr Ser MET Phe Ser MET Glu Cys Val Leu Lys Ile Ile Ala

4672 4681 4690 4699 4708 4717

TTT GGG GTG CTG AAC TAT TTC AGA GAT GCC TGG AAT GTC TTT GAC TTT GTC ACT
Phe Gly Val Leu Asn Tyr Phe Arg Asp Ala Trp Asn Val Phe Asp Phe Val Thr

4726 4735 4744 4753 4762 4771

GTG TTG GGA AGT ATT ACT GAT ATT TTA GTA ACA GAG ATT GCG AAC AAT TTC ATC
Val Leu Gly Ser Ile Thr Asp Ile Leu Val Thr Glu Ile Ala Asn Asn Phe Ile

4780 4789 4798 4807 4816 4825

AAC CTC AGC TTC CTC CGC CTC TTT CGA GCT GCG CGG CTG ATC AAG CTG CTC CGC
Asn Leu Ser Phe Leu Arg Leu Phe Arg Ala Ala Arg Leu Ile Lys Leu Leu Arg

4834 4843 4852 4861 4870 4879

CAG GGC TAC ACC ATC CGC ATC CTG CTG TGG ACC TTT GTC CAG TCC TTC AAG GCC
Gln Gly Tyr Thr Ile Arg Ile Leu Leu Trp Thr Phe Val Gln Ser Phe Lys Ala

4888 4897 4906 4915 4924 4933

CTG CCC TAC GTG TGT CTG CTC ATT GCC ATG CTG TTC TTC ATC TAC GCC ATC ATC
Leu Pro Tyr Val Cys Leu Leu Ile Ala MET Leu Phe Phe Ile Tyr Ala Ile Ile

4942 4951 4960 4969 4978 4987

GGC ATG CAG GTG TTT GGG AAT ATT GCC CTG GAT GAT GAC ACC AGC ATC AAC CGC
Gly MET Gln Val Phe Gly Asn Ile Ala Leu Asp Asp Asp Thr Ser Ile Asn Arg

4996 5005 5014 5023 5032 5041

CAC AAC AAC TTC CGG ACG TTT TTG CAA GCC CTG ATG CTG CTG TTC AGG AGC GCC

His Asn Asn Phe Arg Thr Phe Leu Gln Ala Leu MET Leu Leu Phe Arg Ser Ala

5050 5059 5068 5077 5086 5095

ACG GGG GAG GCC TGG CAC GAG ATC ATG CTG TCC TGC CTG AGC AAC CAG GCC TGT
Thr Gly Glu Ala Trp His Glu Ile MET Leu Ser Cys Leu Ser Asn Gln Ala Cys

5104 5113 5122 5131 5140 5149

GAT GAG CAG GCC AAT GCC ACC GAG TGT GGA AGT GAC TTT GCC TAC TTC TAC TTC
Asp Glu Gln Ala Asn Ala Thr Glu Cys Gly Ser Asp Phe Ala Tyr Phe Tyr Phe

5158 5167 5176 5185 5194 5203

GTC TCC TTC ATC TTC CTG TGC TCC TTT CTG ATG TTG AAC CTC TTT GTG GCT GTG
Val Ser Phe Ile Phe Leu Cys Ser Phe Leu MET Leu Asn Leu Phe Val Ala Val

5212 5221 5230 5239 5248 5257

ATC ATG GAC AAT TTT GAG TAC CTC ACG CGG GAC TCT TCC ATC CTA GGT CCT CAC
Ile MET Asp Asn Phe Glu Tyr Leu Thr Arg Asp Ser Ser Ile Leu Gly Pro His

5266 5275 5284 5293 5302 5311

CAC TTG GAT GAG TTC ATC CGG GTC TGG GCT GAA TAC GAC CCG GCT GCG TGT GGG
His Leu Asp Glu Phe Ile Arg Val Trp Ala Glu Tyr Asp Pro Ala Ala Cys Gly

5320 5329 5338 5347 5356 5365

CGC ATC AGT TAC AAT GAC ATG TTT GAG ATG CTG AAA CAC ATG TCC CCG CCT CTG
Arg Ile Ser Tyr Asn Asp MET Phe Glu MET Leu Lys His MET Ser Pro Pro Leu

5374 5383 5392 5401 5410 5419

GGG CTG GGG AAG AAA TGC CCT GCT CGA GTT GCT TAC AAG CGC CTG GTT CGC ATG
Gly Leu Gly Lys Lys Cys Pro Ala Arg Val Ala Tyr Lys Arg Leu Val Arg MET

5428 5437 5446 5455 5464 5473

AAC ATG CCC ATC TCC AAC GAG GAC ATG ACT GTT CAC TTC ACG TCC ACG CTG ATG
Asn MET Pro Ile Ser Asn Glu Asp MET Thr Val His Phe Thr Ser Thr Leu MET

5482 5491 5500 5509 5518 5527

GCC CTC ATC CGG ACG GCA CTG GAG ATC AAG CTG GCC CCA GCT GGG ACA AAG CAG
Ala Leu Ile Arg Thr Ala Leu Glu Ile Lys Leu Ala Pro Ala Gly Thr Lys Gln

5536 5545 5554 5563 5572 5581

CAT CAG TGT GAC GCG GAG TTG AGG AAG GAG ATT TCC GTT GTG TGG GCC AAT CTG
His Gln Cys Asp Ala Glu Leu Arg Lys Glu Ile Ser Val Val Trp Ala Asn Leu

5590 5599 5608 5617 5626 5635

CCC CAG AAG ACT TTG GAC TTG CTG GTA CCA CCC CAT AAG CCT GAT GAG ATG ACA
Pro Gln Lys Thr Leu Asp Leu Leu Val Pro Pro His Lys Pro Asp Glu MET Thr

5644 5653 5662 5671 5680 5689

GTG GGG AAG GTT TAT GCA GCT CTG ATG ATA TTT GAC TTC TAC AAG CAG AAC AAA

Val Gly Lys Val Tyr Ala Ala Leu MET Ile Phe Asp Phe Tyr Lys Gln Asn Lys

5698 5707 5716 5725 5734 5743

ACC ACC AGA GAC CAG ATG CAG CAG GCT CCT GGA GGC CTC TCC CAG ATG GGT CCT
Thr Thr Arg Asp Gln MET Gln Gln Ala Pro Gly Gly Leu Ser Gln MET Gly Pro

5752 5761 5770 5779 5788 5797

GTG TCC CTG TTC CAC CCT CTG AAG GCC ACC CTG GAG CAG ACA CAG CCG GCT GTG
Val Ser Leu Phe His Pro Leu Lys Ala Thr Leu Glu Gln Thr Gln Pro Ala Val

5806 5815 5824 5833 5842 5851

CTC CGA GGA GCC CGG GTT TTC CTT CGA CAG AAG AGT TCC ACC TCC CTC AGC AAT
Leu Arg Gly Ala Arg Val Phe Leu Arg Gln Lys Ser Ser Thr Ser Leu Ser Asn

5860 5869 5878 5887 5896 5905

GGC GGG GCC ATA CAA AAC CAA GAG AGT GGC ATC AAA GAG TCT GTC TCC TGG GGC
Gly Gly Ala Ile Gln Asn Gln Glu Ser Gly Ile Lys Glu Ser Val Ser Trp Gly

5914 5923 5932 5941 5950 5959

ACT CAA AGG ACC CAG GAT GCA CCC CAT GAG GCC AGG CCA CCC CTG GAG CGT GGC
Thr Gln Arg Thr Gln Asp Ala Pro His Glu Ala Arg Pro Pro Leu Glu Arg Gly

5968 5977 5986 5995 6004 6013

CAC TCC ACA GAG ATC CCT GTG GGG CGG TCA GGA GCA CTG GCT GTG GAC GTT CAG
His Ser Thr Glu Ile Pro Val Gly Arg Ser Gly Ala Leu Ala Val Asp Val Gln

6022 6031 6040 6049 6058 6067

ATG CAG AGC ATA ACC CGG AGG GGC CCT GAT GGG GAG CCC CAG CCT GGG CTG GAG
MET Gln Ser Ile Thr Arg Arg Gly Pro Asp Gly Glu Pro Gln Pro Gly Leu Glu

6076 6085 6094 6103 6112 6121

AGC CAG GGT CGA GCG GCC TCC ATG CCC CGC CTT GCG GCC GAG ACT CAG CCC GTC
Ser Gln Gly Arg Ala Ala Ser MET Pro Arg Leu Ala Ala Glu Thr Gln Pro Val

6130 6139 6148 6157 6166 6175

ACA GAT GCC AGC CCC ATG AAG CGC TCC ATC TCC ACG CTG GCC CAG CGG CCC CGT
Thr Asp Ala Ser Pro MET Lys Arg Ser Ile Ser Thr Leu Ala Gln Arg Pro Arg

6184 6193 6202 6211 6220 6229

GGG ACT CAT CTT TGC AGC ACC ACC CCG GAC CGC CCA CCC CCT AGC CAG GCG TCG
Gly Thr His Leu Cys Ser Thr Thr Pro Asp Arg Pro Pro Pro Ser Gln Ala S r

6238 6247 6256 6265 6274 6283

TCG CAC CAC CAC CAC CAC CGC TGC CAC CGC CGC AGG GAC AGG AAG CAG AGG TCC
Ser His His His His His Arg Cys His Arg Arg Arg Asp Arg Lys Gln Arg S r

6292 6301 6310 6319 6328 6337

CTG GAG AAG GGG CCC AGC CTG TCT GCC GAT ATG GAT GGC GCA CCA AGC AGT GCT

Leu Glu Lys Gly Pro Ser Leu Ser Ala Asp MET Asp Gly Ala Pro Ser Ser Ala

6346 6355 6364 6373 6382 6391

GTG GGG CCG GGG CTG CCC CCG GGA GAG GGG CCT ACA GGC TGC CGG CGG GAA CGA
Val Gly Pro Gly Leu Pro Pro Gly Glu Gly Pro Thr Gly Cys Arg Arg Glu Arg

6400 6409 6418 6427 6436 6445

GAG CGC CGG CAG GAG CGG AGC CGG TCC CAG GAG CGG AGG CAG CCC TCA TCC TCC
Glu Arg Arg Gln Glu Arg Ser Arg Ser Gln Glu Arg Arg Gln Pro Ser Ser Ser

6454 6463 6472 6481 6490 6499

TCC TCG GAG AAG CAG CGC TTC TAC TCC TGC GAC CGC TTT GGG GGC CGT GAG CCC
Ser Ser Glu Lys Gln Arg Phe Tyr Ser Cys Asp Arg Phe Gly Gly Arg Glu Pro

6508 6517 6526 6535 6544 6553

CCG AAG CCC AAG CCC TCC CTC AGC AGC CAC CCA ACG TCG CCA ACA GCT GGC CAG
Pro Lys Pro Lys Pro Ser Leu Ser Ser His Pro Thr Ser Pro Thr Ala Gly Gln

6562 6571 6580 6589 6598 6607

GAG CCG GGA CCC CAC CCA CAG GGC AGT GGT TCC GTG AAT GGG AGC CCC TTG CTG
Glu Pro Gly Pro His Pro Gln Gly Ser Gly Ser Val Asn Gly Ser Pro Leu Leu

6616 6625 6634 6643 6652 6661

TCA ACA TCT GGT GCT AGC ACC CCC GGC CGC GGT GGG CGG AGG CAG CTC CCC CAG
Ser Thr Ser Gly Ala Ser Thr Pro Gly Arg Gly Gly Arg Arg Gln Leu Pro Gln

6670 6679 6688 6697 6706 6715

ACG CCC CTG ACT CCC CGC CCC AGC ATC ACC TAC AAG ACG GCC AAC TCC TCA CCC
Thr Pro Leu Thr Pro Arg Pro Ser Ile Thr Tyr Lys Thr Ala Asn Ser Ser Pro

6724 6733 6742 6751 6760 6769

ATC CAC TTC GCC GGG GCT CAG ACC AGC CTC CCT GCC TTC TCC CCA GGC CGG CTC
Ile His Phe Ala Gly Ala Gln Thr Ser Leu Pro Ala Phe Ser Pro Gly Arg Leu

6778 6787 6796 6805 6814 6823

AGC CGT GGG CTT TCC GAA CAC AAC GCC CTG CTG CAG AGA GAC CCC CTC AGC CAG
Ser Arg Gly Leu Ser Glu His Asn Ala Leu Leu Gln Arg Asp Pro Leu Ser Gln

6832 6841 6850 6859 6868 6877

CCC CTG GCC CCT GGC TCT CGA ATT GGC TCT GAC CCT TAC CTG GGG CAG CGT CTG
Pro Leu Ala Pro Gly Ser Arg Ile Gly Ser Asp Pro Tyr Leu Gly Gln Arg Leu

6886 6895 6904 6913 6922 6931

GAC AGT GAG GCC TCT GTC CAC GCC CTG CCT GAG GAC ACG CTC ACT TTC GAG GAG
Asp Ser Glu Ala Ser Val His Ala Leu Pro Glu Asp Thr Leu Thr Phe Glu Glu

6940 6949 6958 6967 6976 6985

GCT GTG GCC ACC AAC TCG GGC CGC TCC TCC AGG ACT TCC TAC GTG TCC TCC CTG

```
Ala Val Ala Thr Asn Ser Gly Arg Ser Ser Arg Thr Ser Tyr Val Ser Ser Leu

      6994        7003        7012        7021        7030        7039

ACC TCC CAG TCT CAC CCT CTC CGC CGC GTG CCC AAC GGT TAC CAC TGC ACC CTG
Thr Ser Gln Ser His Pro Leu Arg Arg Val Pro Asn Gly Tyr His Cys Thr Leu

      7048        7057        7066        7075        7084        7093

GGA CTC AGC TCG GGT GGC CGA GCA CGG CAC AGC TAC CAC CAC CCT GAC CAA GAC
Gly Leu Ser Ser Gly Gly Arg Ala Arg His Ser Tyr His His Pro Asp Gln Asp

      7102        7115        7125        7135        7145        7155

CAC TGG TGC TAG CTGCACCGTG ACCGCTCAGA CGCCTGCATG CAGCAGGCGT GTGTTCCAGT
His Trp Cys

      7165        7175        7185        7195        7205        7215        72:

GGATGAGTTT TATCATCCAC ACGGGGCAGT CGGCCCTCGG GGGAGGCCTT GCCCACCTTG GTGAGGCT

      7235        7245        7255        7265

TGTGGCCCCT CCCTCCCCCT CCTCCCCTCT TTTACTCTAG A


RANSLATE [Partial]: q

EQ: rec

nd recording to seq.rec? (<CR>=Yes)

nding recording for user SHUEYD at 7-Mar-95 3:22pm
```

utilizes the universal genetic code unless modified with the EDIT-CODONS command.

ACHALPHA2

Frame-1:	745:774	1354:1440	1786:1938	
Frame-2:	20:3295			
Frame-3:	201:257	378:455	474:560	561:587
	588:662	726:800	1062:1277	1302:1328
	1362:1427	1491:1520	1545:1634	1665:1697
	1701:1856	2106:2171	2193:2288	2292:2366
	2574:2630	2658:2756	2868:2966	3153:3215

Would you like to see the display of open reading frames? (<CR>=No)

ACHALPHA2' - Numbering increases in 5' to 3' direction

Frame-4:	304:336	568:612	724:831	2779:3177
Frame-5:	62:115	179:307	392:616	1874:2011
	2519:2575	2765:2797	2831:2908	3224:END
Frame-6:	240:272	348:392	549:635	1041:1097
	1227:1259	1338:1502	1512:1562	1575:1628
	1662:1730	1920:1958	2400:2474	2532:2702
	2976:2999			

Would you like to see the display of open reading frames? (<CR>=No)

Segment from ACHALPHA2 (1 to 3298) to be translated: 20 3295

Segment from ACHALPHA2 (1 to 3298) to be translated:

```
          10         19          28          37          46          55
TTGATCTTCG ATCGCGAAG >ATG GCT GCT GGC TGC CTG CTG GCC TTG ACT CTG ACA
                      MET Ala Ala Gly Cys Leu Leu Ala Leu Thr Leu Thr

          64         73          82          91          100         109
CTT TTC CAA TCT TTG CTC ATC GGC CCC TCG TCG GAG GAG CCG TTC CCT TCG GCC
Leu Phe Gln Ser L u Leu Ile Gly Pro Ser Ser Glu Glu Pro Phe Pro Ser Ala

     118         127         136         145         154         163
GTC ACT ATC AAA TCA TGG GTG GAT AAG ATG CAA GAA GAC CTT GTC ACA CTG GCA
```

FIG. 2

```
Val Thr Ile Lys Ser Trp Val Asp Lys MET Gln Glu Asp Leu Val Thr Leu Ala
        172       181       190       199       208       217
AAA ACA GCA AGT GGA GTC AAT CAG CTT GTT GAT ATT TAT GAG AAA TAT CAA GAT
Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr Gln Asp
        226       235       244       253       262       271
TTG TAT ACT GTG GAA CCA AAT AAT GCA CGC CAG CTG GTA GAA ATT GCA GCC AGG
Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu Ile Ala Ala Arg
        280       289       298       307       316       325
GAT ATT GAG AAA CTT CTG AGC AAC AGA TCT AAA GCC CTG GTG AGC CTG GCA TTG
Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala Leu Val Ser Leu Ala Leu
        334       343       352       361       370       379
GAA GCG GAG AAA GTT CAA GCA GCT CAC CAG TGG AGA GAA GAT TTT GCA AGC AAT
Glu Ala Glu Lys Val Gln Ala Ala His Gln Trp Arg Glu Asp Phe Ala Ser Asn
        388       397       406       415       424       433
GAA GTT GTC TAC TAC AAT GCA AAG GAT GAT CTC GAT CCT GAG AAA AAT GAC AGT
Glu Val Val Tyr Tyr Asn Ala Lys Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser
        442       451       460       469       478       487
GAG CCA GGC AGC CAG AGG ATA AAA CCT GTT TTC ATT GAA GAT GCT AAT TTT GGA
Glu Pro Gly Ser Gln Arg Ile Lys Pro Val Phe Ile Glu Asp Ala Asn Phe Gly
        496       505       514       523       532       541
CGA CAA ATA TCT TAT CAG CAC GCA GCA GTC CAT ATT CCT ACT GAC ATC TAT GAG
Arg Gln Ile Ser Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu
        550       559       568       577       586       595
GGC TCA ACA ATT GTG TTA AAT GAA CTC AAC TGG ACA AGT GCC TTA GAT GAA GTT
Gly Ser Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
        604       613       622       631       640       649
TTC AAA AAG AAT CGC GAG GAA GAC CCT TCA TTA TTG TGG CAG GTT TTT GGC AGT
Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe Gly Ser
        658       667       676       685       694       703
GCC ACT GGC CTA GCT CGA TAT TAT CCA GCT TCA CCA TGG GTT GAT AAT AGT AGA
Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val Asp Asn Ser Arg
        712       721       730       739       748       757
ACT CCA AAT AAG ATT GAC CTT TAT GAT GTA CGC AGA AGA CCA TGG TAC ATC CAA
Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg Arg Pro Trp Tyr Ile Gln
    ----
    ---- 766       775       784       793       802       811
GGA GCT GCA TCT CCT AAA GAC ATG CTT ATT CTG GTG GAT GTG AGT GGA AGT GTT
```

Gly Ala Ala Ser Pro Lys Asp MET Leu Ile Leu Val Asp Val Ser Gly Ser Val

820 829 838 847 856 865

AGT GGA TTG ACA CTT AAA CTG ATC CGA ACA TCT GTC TCC GAA ATG TTA GAA ACC
Ser Gly Leu Thr Leu Lys Leu Ile Arg Thr Ser Val Ser Glu MET Leu Glu Thr

874 883 892 901 910 919

CTC TCA GAT GAT GAT TTC GTG AAT GTA GCT TCA TTT AAC AGC AAT GCT CAG GAT
Leu Ser Asp Asp Asp Phe Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp

928 937 946 955 964 973

GTA AGC TGT TTT CAG CAC CTT GTC CAA GCA AAT GTA AGA AAT AAA AAA GTG TTG
Val Ser Cys Phe Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu

982 991 1000 1009 1018 1027

AAA GAC GCG GTG AAT AAT ATC ACA GCC AAA GGA ATT ACA GAT TAT AAG AAG GGC
Lys Asp Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly

1036 1045 1054 1063 1072 1081

TTT AGT TTT GCT TTT GAA CAG CTG CTT AAT TAT AAT GTT TCC AGA GCA AAC TGC
Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala Asn Cys

1090 1099 1108 1117 1126 1135

AAT AAG ATT ATT ATG CTA TTC ACG GAT GGA GGA GAA GAG AGA GCC CAG GAG ATA
Asn Lys Ile Ile MET Leu Phe Thr Asp Gly Gly Glu Glu Arg Ala Gln Glu Ile

1144 1153 1162 1171 1180 1189

TTT AAC AAA TAC AAT AAA GAT AAA AAA GTA CGT GTA TTC AGG TTT TCA GTT GGT
Phe Asn Lys Tyr Asn Lys Asp Lys Lys Val Arg Val Phe Arg Phe Ser Val Gly

1198 1207 1216 1225 1234 1243

CAA CAC AAT TAT GAG AGA GGA CCT ATT CAG TGG ATG GCC TGT GAA AAC AAA GGT
Gln His Asn Tyr Glu Arg Gly Pro Ile Gln Trp MET Ala Cys Glu Asn Lys Gly

1252 1261 1270 1279 1288 1297

TAT TAT TAT GAA ATT CCT TCC ATT GGT GCA ATA AGA ATC AAT ACT CAG GAA TAT
Tyr Tyr Tyr Glu Ile Pro Ser Ile Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr

1306 1315 1324 1333 1342 1351

TTG GAT GTT TTG GGA AGA CCA ATG GTT TTA GCA GGA GAC AAA GCT AAG CAA GTC
Leu Asp Val Leu Gly Arg Pro MET Val Leu Ala Gly Asp Lys Ala Lys Gln Val

1360 1369 1378 1387 1396 1405

CAA TGG ACA AAT GTG TAC CTG GAT GCA TTG GAA CTG GGA CTT GTC ATT ACT GGA
Gln Trp Thr Asn Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly

1414 1423 1432 1441 1450 1459

ACT CTT CCG GTC TTC AAC ATA ACC GGC CAA TTT GAA AAT AAG ACA AAC TTA AAG

Thr Leu Pro Val Phe Asn Ile Thr Gly Gln Phe Glu Asn Lys Thr Asn Leu Lys

1468 1477 1486 1495 1504 1513

AAC CAG CTG ATT CTT GGT GTG ATG GGA GTA GAT GTG TCT TTG GAA GAT ATT AAA
Asn Gln Leu Ile Leu Gly Val MET Gly Val Asp Val Ser Leu Glu Asp Ile Lys

1522 1531 1540 1549 1558 1567

AGA CTG ACA CCA CGT TTT ACA CTG TGC CCC AAT GGG TAT TAC TTT GCA ATC GAT
Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr Phe Ala Ile Asp

1576 1585 1594 1603 1612 1621

CCT AAT GGT TAT GTT TTA TTA CAT CCA AAT CTT CAG CCA AAG AAC CCC AAA TCT
Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln Pro Lys Asn Pro Lys Ser

1630 1639 1648 1657 1666 1675

CAG GAG CCA GTA ACA TTG GAT TTC CTT GAT GCA GAG TTA GAG AAT GAT ATT AAA
Gln Glu Pro Val Thr Leu Asp Phe Leu Asp Ala Glu Leu Glu Asn Asp Ile Lys

1684 1693 1702 1711 1720 1729

GTG GAG ATT CGA AAT AAG ATG ATT GAT GGG GAA AGT GGA GAA AAA ACA TTC AGA
Val Glu Ile Arg Asn Lys MET Ile Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg

1738 1747 1756 1765 1774 1783

ACT CTG GTT AAA TCT CAA GAT GAG AGA TAT ATT GAC AAA GGA AAC AGG ACA TAC
Thr Leu Val Lys Ser Gln Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr

1792 1801 1810 1819 1828 1837

ACA TGG ACA CCT GTC AAT GGC ACA GAT TAC AGT TTG GCC TTG GTA TTA CCA ACC
Thr Trp Thr Pro Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr

1846 1855 1864 1873 1882 1891

TAC AGT TTT TAC TAT ATA AAA GCC AAA CTA GAA GAG ACA ATA ACT CAG GCC AGA
Tyr Ser Phe Tyr Tyr Ile Lys Ala Lys Leu Glu Glu Thr Ile Thr Gln Ala Arg

1900 1909 1918 1927 1936 1945

TCA AAA AAG GGC AAA ATG AAG GAT TCG GAA ACC CTG AAG CCA GAT AAT TTT GAA
Ser Lys Lys Gly Lys MET Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn Phe Glu

1954 1963 1972 1981 1990 1999

GAA TCT GGC TAT ACA TTC ATA GCA CCA AGA GAT TAC TGC AAT GAC CTG AAA ATA
Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn Asp Leu Lys Ile

2008 2017 2026 2035 2044 2053.

TCG GAT AAT AAC ACT GAA TTT CTT TTA AAT TTC AAC GAG TTT ATT GAT AGA AAA
Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn Glu Phe Ile Asp Arg Lys

2062 2071 2080 2089 2098 2107

ACT CCA AAC AAC CCA TCA TGT AAC GCG GAT TTG ATT AAT AGA GTC TTG CTT GAT

Thr Pro Asn Asn Pro Ser Cys Asn Ala Asp Leu Ile Asn Arg Val Leu Leu Asp

2116 2125 2134 2143 2152 2161

GCA GGC TTT ACA AAT GAA CTT GTC CAA AAT TAC TGG AGT AAG CAG AAA AAT ATC
Ala Gly Phe Thr Asn Glu Leu Val Gln Asn Tyr Trp Ser Lys Gln Lys Asn Il

2170 2179 2188 2197 2206 2215

AAG GGA GTG AAA GCA CGA TTT GTT GTG ACT GAT GGT GGG ATT ACC AGA GTT TAT
Lys Gly Val Lys Ala Arg Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr

2224 2233 2242 2251 2260 2269

CCC AAA GAG GCT GGA GAA AAT TGG CAA GAA AAC CCA GAG ACA TAT GAG GAC AGC
Pro Lys Glu Ala Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser

2278 2287 2296 2305 2314 2323

TTC TAT AAA AGG AGC CTA GAT AAT GAT AAC TAT GTT TTC ACT GCT CCC TAC TTT
Phe Tyr Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe

2332 2341 2350 2359 2368 2377

AAC AAA AGT GGA CCT GGT GCC TAT GAA TCG GGC ATT ATG GTA AGC AAA GCT GTA
Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile MET Val Ser Lys Ala Val

2386 2395 2404 2413 2422 2431

GAA ATA TAT ATT CAA GGG AAA CTT CTT AAA CCT GCA GTT GTT GGA ATT AAA ATT
Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val Gly Ile Lys Ile

2440 2449 2458 2467 2476 2485

GAT GTA AAT TCC TGG ATA GAG AAT TTC ACC AAA ACC TCA ATC AGA GAT CCG TGT
Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr Ser Ile Arg Asp Pro Cys

2494 2503 2512 2521 2530 2539

GCT GGT CCA GTT TGT GAC TGC AAA AGA AAC AGT GAC GTA ATG GAT TGT GTG ATT
Ala Gly Pro Val Cys Asp Cys Lys Arg Asn Ser Asp Val MET Asp Cys Val Ile

2548 2557 2566 2575 2584 2593

CTG GAT GAT GGT GGG TTT CTT CTG ATG GCA AAT CAT GAT GAT TAT ACT AAT CAG
Leu Asp Asp Gly Gly Phe Leu Leu MET Ala Asn His Asp Asp Tyr Thr Asn Gln

2602 2611 2620 2629 2638 2647

ATT GGA AGA TTT TTT GGA GAG ATT GAT CCC AGC TTG ATG AGA CAC CTG GTT AAT
Ile Gly Arg Phe Phe Gly Glu Ile Asp Pro Ser Leu MET Arg His Leu Val Asn

2656 2665 2674 2683 2692 2701

ATA TCA GTT TAT GCT TTT AAC AAA TCT TAT GAT TAT CAG TCA GTA TGT GAG CCC
Ile Ser Val Tyr Ala Ph Asn Lys Ser Tyr Asp Tyr Gln S r Val Cys Glu Pro

2710 2719 2728 2737 2746 2755

GGT GCT GCA CCA AAA CAA GGA GCA GGA CAT CGC TCA GCA TAT GTG CCA TCA GTA

```
Gly Ala Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Val

      2764        2773        2782        2791        2800        2809

GCA GAC ATA TTA CAA ATT GGC TGG TGG GCC ACT GCT GCT GCC TGG TCT ATT CTA
Ala Asp Ile Leu Gln Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser Ile Leu

      2818        2827        2836        2845        2854        2863

CAG CAG TTT CTC TTG AGT TTG ACC TTT CCA CGA CTC CTT GAG GCA GTT GAG ATG
Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu Ala Val Glu MET

      2872        2881        2890        2899        2908        2917

GAG GAT GAT GAC TTC ACG GCC TCC CTG TCC AAG CAG AGC TGC ATT ACT GAA CAA
Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln Ser Cys Ile Thr Glu Gln

      2926        2935        2944        2953        2962        2971

ACC CAG TAT TTC TTC GAT AAC GAC AGT AAA TCA TTC AGT GGT GTA TTA GAC TGT
Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys Ser Phe Ser Gly Val Leu Asp Cys

      2980        2989        2998        3007        3016        3025

GGA AAC TGT TCC AGA ATC TTT CAT GGA GAA AAG CTT ATG AAC ACC AAC TTA ATA
Gly Asn Cys Ser Arg Ile Phe His Gly Glu Lys Leu MET Asn Thr Asn Leu Ile

      3034        3043        3052        3061        3070        3079

TTC ATA ATG GTT GAG AGC AAA GGG ACA TGT CCA TGT GAC ACA CGA CTG CTC ATA
Phe Ile MET Val Glu Ser Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile

      3088        3097        3106        3115        3124        3133

CAA GCG GAG CAG ACT TCT GAC GGT CCA AAT CCT TGT GAC ATG GTT AAG CAA CCT
Gln Ala Glu Gln Thr Ser Asp Gly Pro Asn Pro Cys Asp MET Val Lys Gln Pro

      3142        3151        3160        3169        3178        3187

AGA TAC CGA AAA GGG CCT GAT GTC TGC TTT GAT AAC AAT GTC TTG GAG GAT TAT
Arg Tyr Arg Lys Gly Pro Asp Val Cys Phe Asp Asn Asn Val Leu Glu Asp Tyr

      3196        3205        3214        3223        3232        3241

ACT GAC TGT GGT GGT GTT TCT GGA TTA AAT CCC TCC CTG TGG TAT ATC ATT GGA
Thr Asp Cys Gly Gly Val Ser Gly Leu Asn Pro Ser Leu Trp Tyr Ile Ile Gly

      3250        3259        3268        3277        3286        3295

ATC CAG TTT CTA CTA CTT TGG CTG GTA TCT GGC AGC ACA CAC CGG CTG TTA TGA
Ile Gln Phe Leu Leu Leu Trp Leu Val Ser Gly Ser Thr His Arg Leu Leu

CCT
```

Segment from DSHBETA3 (1 to 1476) to be translated:

```
                10        19        28        37        46        55
                >
CTCCCCC ATG TAT GAC GAC TCC TAC GTG CCC GGG TTT GAG GAC TCG GAG GCG GGT
        MET Tyr Asp Asp Ser Tyr Val Pro Gly Phe Glu Asp Ser Glu Ala Gly

                64        73        82        91       100       109
TCA GCC GAC TCC TAC ACC AGC CGC CCA TCT CTG GAC TCA GAC GTC TCC CTG GAG
Ser Ala Asp Ser Tyr Thr Ser Arg Pro Ser Leu Asp Ser Asp Val Ser Leu Glu

               118       127       136       145       154       163
GAG GAC CGG GAG AGT GCC CGG CGT GAA GTA GAG AGC CAG GCT CAG CAG CAG CTC
Glu Asp Arg Glu Ser Ala Arg Arg Glu Val Glu Ser Gln Ala Gln Gln Gln Leu

               172       181       190       199       208       217
GAA AGG GCC AAG CAC AAA CCT GTG GCA TTT GCG GTG AGG ACC AAT GTC AGC TAC
Glu Arg Ala Lys His Lys Pro Val Ala Phe Ala Val Arg Thr Asn Val Ser Tyr

               226       235       244       253       262       271
TGT GGC GTA CTG GAT GAG GAG TGC CCA GTC CAG GGC TCT GGA GTC AAC TTT GAG
Cys Gly Val Leu Asp Glu Glu Cys Pro Val Gln Gly Ser Gly Val Asn Phe Glu

               280       289       298       307       316       325
GCC AAA GAT TTT CTG CAC ATT AAA GAG AAG TAC AGC AAT GAC TGG TGG ATC GGG
Ala Lys Asp Phe Leu His Ile Lys Glu Lys Tyr Ser Asn Asp Trp Trp Ile Gly

               334       343       352       361       370       379
CGG CTA GTG AAA GAG GGC GGG GAC ATC GCC TTC ATC CCC AGC CCC CAG CGC CTG
Arg Leu Val Lys Glu Gly Gly Asp Ile Ala Phe Ile Pro Ser Pro Gln Arg Leu

               388       397       406       415       424       433
GAG AGC ATC CGG CTC AAA CAG GAG CAG AAG GCC AGG AGA TCT GGG AAC CCT TCC
Glu Ser Ile Arg Leu Lys Gln Glu Gln Lys Ala Arg Arg Ser Gly Asn Pro Ser

               442       451       460       469       478       487
AGC CTG AGT GAC ATT GGC AAC CGA CGC TCC CCT CCG CCA TCT CTA GCC AAG CAG
Ser Leu Ser Asp Ile Gly Asn Arg Arg Ser Pro Pro Pro Ser Leu Ala Lys Gln

               496       505       514       523       532       541
AAG CAA AAG CAG GCG GAA CAT GTT CCC CCA TAT GAC GTG GTG CCC TCC ATG CGG
Lys Gln Lys Gln Ala Glu His Val Pro Pro Tyr Asp Val Val Pro Ser MET Arg

               550       559       568       577       586       595
CCT GTG GTG CTG GTG GGA CCC TCT CTG AAA GGT TAT GAG GTC ACA GAC ATG ATG
Pro Val Val Leu Val Gly Pro Ser Leu Lys Gly Tyr Glu Val Thr Asp MET MET

               604       613       622       631       640       649
```

FIG. 3

```
CAG AAG GCT CTC TTC GAC TTC CTC AAA CAC AGA TTT GAT GGC AGG ATC TCC ATC
Gln Lys Ala Leu Phe Asp Phe Leu Lys His Arg Phe Asp Gly Arg Ile Ser Il

       658       667       676       685       694       703

ACC CGA GTC ACA GCC GAC CTC TCC CTG GCA AAG CGA TCT GTG CTC AAC AAT CCG
Thr Arg Val Thr Ala Asp Leu Ser Leu Ala Lys Arg Ser Val Leu Asn Asn Pro

       712       721       730       739       748       757

GGC AAG AGG ACC ATC ATT GAG CGC TCC TCT GCC CGC TCC AGC ATT GCG GAA GTG
Gly Lys Arg Thr Ile Ile Glu Arg Ser Ser Ala Arg Ser Ser Ile Ala Glu Val

       766       775       784       793       802       811

CAG AGT GAG ATC GAG CGC ATA TTT GAG CTG GCC AAA TCC CTG CAG CTA GTA GTG
Gln Ser Glu Ile Glu Arg Ile Phe Glu Leu Ala Lys Ser Leu Gln Leu Val Val

       820       829       838       847       856       865

TTG GAC GCT GAC ACC ATC AAC CAC CCA GCA CAG CTG GCC AAG ACC TCG CTG GCC
Leu Asp Ala Asp Thr Ile Asn His Pro Ala Gln Leu Ala Lys Thr Ser Leu Ala

       874       883       892       901       910       919

CCC ATC ATC GTC TTT GTC AAA GTG TCC TCA CCA AAG GTA CTC CAG CGT CTC ATT
Pro Ile Ile Val Phe Val Lys Val Ser Ser Pro Lys Val Leu Gln Arg Leu Ile

       928       937       946       955       964       973

CGC TCC CGG GGG AAG TCA CAG ATG AAG CAC CTG ACC GTA CAG ATG ATG GCA TAT
Arg Ser Arg Gly Lys Ser Gln MET Lys His Leu Thr Val Gln MET MET Ala Tyr

       982       991      1000      1009      1018      1027

GAT AAG CTG GTT CAG TGC CCA CCG GAG TCA TTT GAT GTG ATT CTG GAT GAG AAC
Asp Lys Leu Val Gln Cys Pro Pro Glu Ser Phe Asp Val Ile Leu Asp Glu Asn

      1036      1045      1054      1063      1072      1081

CAG CTG GAG GAT GCC TGT GAG CAC CTG GCT GAG TAC CTG GAG GTT TAC TGG CGG
Gln Leu Glu Asp Ala Cys Glu His Leu Ala Glu Tyr Leu Glu Val Tyr Trp Arg

      1090      1099      1108      1117      1126      1135

GCC ACG CAC CAC CCA GCC CCT GGC CCC GGA CTT CTG GGT CCT CCC AGT GCC ATC
Ala Thr His His Pro Ala Pro Gly Pro Gly Leu Leu Gly Pro Pro Ser Ala Ile

      1144      1153      1162      1171      1180      1189

CCC GGA CTT CAG AAC CAG CAG CTG CTG GGG GAG CGT GGC GAG GAG CAC TCC CCC
Pro Gly Leu Gln Asn Gln Gln Leu Leu Gly Glu Arg Gly Glu Glu His Ser Pro

      1198      1207      1216      1225      1234      1243

CTT GAG CGG GAC AGC TTG ATG CCC TCT GAT GAG GCC AGC GAG AGC TCC CGC CAA
Leu Glu Arg Asp Ser Leu MET Pro Ser Asp Glu Ala Ser Glu Ser Ser Arg Gln

      1252      1261      1270      1279      1288      1297
```

```
GCC TGG ACA GGA TCT TCA CAG CGT AGC TCC CGC CAC CTG GAG GAG GAC TAT GCA
Ala Trp Thr Gly Ser Ser Gln Arg Ser Ser Arg His Leu Glu Glu Asp Tyr Ala

      1306        1315        1324        1333        1342        1351

GAT GCC TAC CAG GAC CTG TAC CAG CCT CAC CGC CAA CAC ACC TCG GGG CTG CCT
Asp Ala Tyr Gln Asp Leu Tyr Gln Pro His Arg Gln His Thr Ser Gly Leu Pro

      1360        1369        1378        1387        1396        1405

AGT GCT AAC GGG CAT GAC CCC CAA GAC CGG CTT CTA GCC CAG GAC TCA GAA CAC
Ser Ala Asn Gly His Asp Pro Gln Asp Arg Leu Leu Ala Gln Asp Ser Glu His

      1414        1423        1432        1441        1450        1459

AAC CAC AGT GAC CGG AAC TGG CAG CGC AAC CGG CCT TGG CCC AAG GAT AGC TAC
Asn His Ser Asp Arg Asn Trp Gln Arg Asn Arg Pro Trp Pro Lys Asp Ser Tyr

      1472

TGA CAGCCTCCTG CTGC
```

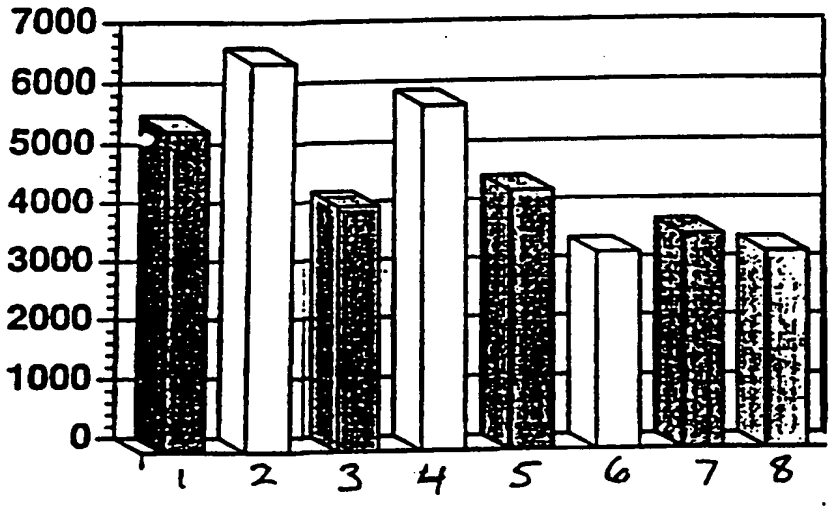

FIG. 4

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(71) Applicant (*for all designated States except US*): AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07940 (US).

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(75) Inventors/Applicants (*for US only*): FRANCO, Rodrigo [–/US]; 46 Liberty Ridge Road, Basking Ridge, NJ 07920 (US). CHEN, Ai, Ru, Sun [–/US]; 119 Marvin Lane, Piscataway, NJ 08854 (US). SHUEY, David, John [–/US]; 1409 Hunters Glen, Plainsboro, NJ 08536 (US).

(74) Agents: WALSH, Andrea, C. et al.; American Home Products Corporation, Patent Law Dept.-2B, One Campus Drive, Parsippany, NJ 07054 (US).

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(57) Abstract

Nucleic acids encoding each of three subunits, a1B, a2d, and b3, of a calcium channel, are disclosed. Also disclosed are vectors containing the nucleic acids encoding the subunits; host cells containing the nucleic acids encoding the subunits; methods of isolating nucleic acids encoding related calcium channel subunits; the subunit proteins; fusion proteins comprising the subunit proteins; antibodies to the subunit proteins; assays to identify agents that modulate calcium channel activity, and agents identified thereby; methods f treating certain central nervous system disorders by altering calcium channel activity; and methods of diagnosing diseases associated with particular calcium channels, such as Lambert-Eaton syndrome.

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INTERNATIONAL SEARCH REPORT

Intern. nal Application No
PCT/US 97/16146

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/705 C07K16/18 G01N33/53

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 04822 A (THE SALK INSTITUTE) 16 February 1995 * claims; description p. 1-10; SEQ ID NOs: 7, 8, 9, 11, 19, 20, 29-32 * ---	1-19
X	WO 93 04083 A (THE SALK INSTITUTE) 4 March 1993 * claims; pages 1-23; SEQ ID NOs 7;11 * ---	1-6, 12-14, 18,19
X	WILLIAMS, M.E. ET AL.: "Structure nd functional expression ..." SCIENCE, vol. 257, 1992, pages 389-394, XP002056227 * fig. 1, seq 1B-1 * --- -/--	1,6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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1

Date of the actual completion of the international search	Date of mailing of the international search report
5 May 1998	29.05.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hermann, R

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INTERNATIONAL SEARCH REPORT

Interr. nal Application No
PCT/US 97/16146

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DUBEL, S.J. ET AL.: "Molecular cloning of the alpha-1 subunit ..." PROC. NATL. ACAD. SCI. USA, vol. 89, 1992, pages 5058-5062, XP002056228 * fig. 1 *	13
X	CHEN, A. ET AL.: "Molecular characterization ..." SOC. NEUROSCI. ABS., vol. 20, no. 1-2, 1994, page 68 XP002056229 * abstract 34.10 *	1-6, 12-14,19
X	SHUEY, D. ET AL.: "Structure/function studies ..." SOC. NEUROSCI. ABS., vol. 21, no. 1-3, 1995, page 1573 XP002056230 * abstract 618.4 *	1-6, 12-14,19
X	EP 0 556 651 A (BAYER AG) 25 August 1993 * claims; pages 9-11 *	7-11, 15-17,19
X	MURAKAMI, M. ET AL.: "Gene structure of the murine calcium channel ..." EUR. J. BIOCHEM., vol. 236, 1996, pages 138-143, XP002064078 * figs. 2 and 3 *	7-11, 15-17,19
X	ANGELOTTI, T. & HOFMANN, F.: "Tissue specific expression of splice-variants ..." FEBS LETTERS, vol. 397, 1996, pages 331-337, XP002064079 * figs. 1 and 2 *	18
X	WILLIAMS, M.E. ET AL.: "Structure and functional expression ..." NEURON, vol. 8, 1992, pages 71-84, XP002064080 * figure 3 *	18

1

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INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 97/ 16146

B x I Observations where certain claims were found unsearchable (Continuati n of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See further information sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See separate sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-6,12-14, 19(part)

Calcium channel a1B subunit, and related subject-matter (coding DNA, vector, host cell, antibody, fusion protein, method)

2. Claims: 7-11,15-17, 19(part)

Calcium channel b3 subunit, and related subject-matter (coding DNA, vector, host cell, antibody, fusion protein, method)

3. Claim : 18

An isolated calcium channel, comprising subunits encoded by sequences of SEQ ID NOs. 1,3,5.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 20; parts of 1,2,4-17,19

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

CLAIM 20: A compound is not characterised by a method for its identification.
CLAIMS 1,2,4-17,19: The positions of almost all nucleotide exchanges or insertions referred to in said claims do obviously not correspond to the sequence listing: the nucleotides in the indicated positions scarcely correspond to the original, or to the modified nucleotide; in the few cases where the nucleotide is accidentally correct, the encoded amino acids differ from those indicated in the tables I and III. Apart from the only correctly indicated nucleic acid exchange in position 2559 of the a1B subunit (SEQ ID NO. 1), which has been searched as such, the searches for the three different inventions have been restricted to the nucleic acid sequences of SEQ ID NOs 1,3,5, the encoded proteins, and related subject-matter, and to the general concept of (unspecified) variations in these sequences.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna..ial Application No
PCT/US 97/16146

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